JOHN E. FOGARTY
INTERNATIONAL
CENTER
FOR ADVANCED
STUDY IN THE
HEALTH SCIENCES

National Institutes of Health Annual Report of International Activities

Fiscal Year 1987

U.S. DEPARTMENT OF
HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes of Health

JOHN E. FOGARTY
INTERNATIONAL
CENTER
FOR ADVANCED
STUDY IN THE
HEALTH SCIENCES

National Institutes of Health Annual Report of International Activities

Fiscal Year 1987

Prepared by
John E. Fogarty
International Center for
Advanced Study in the
Health Sciences

For Administrative Use Only

U.S. DEPARTMENT OF
HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes of Health

Contents

	Page
FOREWORD	vii
I. Overview of International Activities	1
II. Office of the Director	17
III. John E. Fogarty International Center for Advanced Study in the Health Sciences	23
IV. National Cancer Institute	35
V. National Eye Institute	43
VI. National Heart, Lung, and Blood Institute	49
VII. National Institute of Allergy and Infectious Diseases	69
VIII. National Institute of Arthritis and musculoskeletal and Skin Diseases	91
IX. National Institute of Child Health and Human Development	97
X. National Institute of Dental Research	109
XI. National Institute of Diabetes and Digestive and Kidney Diseases	117
XII. National Institute of Environmental Health Sciences	131
XIII. National Institute of General Medical Sciences	137
XIV. National Institute of Neurological and Communicative Disorders and Stroke	139
XV. National Institute on Aging	145
XVI. National Library of Medicine	151
XVII. Warren Grant Magnuson Clinical Center	155
XVIII. National Center for Nursing Research	157
XIX. Division of Computer Research and Technology	159
XX. Division of Research Resources	161
XXI. Division of Research Services	163
APPENDIX A. List of Acronyms	167
APPENDIX B. Definitions of NIH International Program Activities	175
Index by Country/Area	177
Index by International Organization	181
Index by Research Area	183

TABLE

I–1. Total Expenditures for NIH Int'l Programs, by Activity and NIH Component, FY 1987 . . . 2
I–2. International Agreements Involving the NIH . . . 6
I–3. NIH Int'l Research and Research Training Awards by Country/Area and Mechanism, FY 1987 . . . 8
I–4. NIH Int'l Research and Research Training Awards, FY 1947–87 . . . 12
III–1. Senior Int'l Fellowship Awards by Country/Area of Applicants, FY 1987 . . . 27
III–2. Int'l Research Fellowship Awards by Country/Area of Applicants, FY 1987 . . . 28
III–3. Exchanges of U.S. and Foreign Scientists Since Initiation of Programs and FY 1987 . . . 29
III–4. NIH Visiting Program Participants, FY 1987 Rank Order by Country/Area, All Institutes . . . 32
III–5. Foreign Guest Researchers, FY 1987 Rank Order by Country/Area, All Institutes . . . 33
IV–1. NCI Int'l Conferences, Seminars, and Meetings, FY 1987 . . . 40
VI–1. National Heart, Lung, and Blood Institute Int'l Programs, FY 1987 . . . 53
VI–2. National Heart, Lung, and Blood Institute Int'l Programs, Direct Costs, FY 1987 . . . 55
VII–1. ICIDR Program Awards, FY 1987 . . . 89
VII–2. Tropical Disease Research Unit Awards, FY 1987 . . . 89
VII–3. NIAID Int'l Conferences, Seminars, and Meetings, FY 1987 . . . 90
XV–1. NIA Grants to Foreign Institutions, FY 1987 . . . 147
XV–2. NIA Grants to U.S. Investigators, FY 1987 . . . 148
XVI–1. Services Provided in Int'l MEDLARS Centers . . . 151

FIGURE

I–1. NIH Int'l Activities, Funding by Mechanism, FY 1987 . . . 1
I–2. NIH Int'l Research and Research Training Awards, FY 1978–87 . . . 4
I–3. Components of the National Institutes of Health . . . 16
VI–1. Percent Change in Age-Adjusted Death Rates for Coronary Heart Disease, Cerebrovascular Diseases, and Noncardiovascular Causes of Death, U.S., 1950–85 . . . 50

VI–2a. Death Rate for all Causes and Cardiovascular Diseases, Men ages 35–74 in Selected Countries, 1982 51

VI–2b. Death Rate for all Causes and Cardiovascular Diseases, Women ages 35–74 in Selected Countries, 1982 51

VI–3a. Percent Change in Death Rate for Cardiovascular Disease, Men ages 45–54 in Selected Countries, 1970–82 52

VI–3b. Percent Change in Death Rate for Cardiovascular Disease, Women ages 45–54 in Selected Countries, 1970–82 52

Foreword

The John E. Fogarty International Center for Advanced Study in the Health Sciences is pleased to present this *National Institutes of Health Annual Report of International Activities* for fiscal year 1987. It is based on summaries prepared by all the NIH components that are involved in international activities.

The NIH celebrated its Centennial throughout 1987, and four special Centennial events international in scope were held in the United States in FY 1987. Eight Centennial events were hosted by foreign countries abroad. These celebrations represent the international cooperation to improve world health in which the NIH plays an important role.

Collaborative research between U.S. and foreign scientists through NIH programs exists in many areas, including AIDS, Alzheimer's disease, cancer, cardiovascular diseases, cataract blindness, diabetes mellitus, Down syndrome, and stroke.

The report contains a summary of all NIH-supported international research by country, research institute, and funding. There are indices by country, international organization, and research area.

We hope the report is useful, and we would appreciate any suggestions on how future editions might be modified to better serve your interests and needs.

Carl Kupfer, M.D.
Acting Director
Fogarty International Center

Table I–1

TOTAL EXPENDITURES FOR NIH INTERNATIONAL PROGRAMS, BY ACTIVITY AND NIH COMPONENT, FY 1987
(in thousands of dollars)

	OD	NCI	NHLBI	NIDDK	NLM	NIA	NIAID	NIAMS	NICHD	NIDR	NIEHS	NEI
I. Research Awards												
A. Grants												
Foreign Research Grants	—	3,757	1,982	2,197	70	504	829	65	1,027	386	233	829
Cooperative Agreement Awards	—	2,017	15	610	—	—	—	—	—	—	683	394
Core Grant to Gorgas Memorial Institute[a]	—	—	—	—	—	—	—	—	—	—	—	—
Foreign Components of Domestic Grants	—	1,303	441	451	—	709	1,347	122	973	144	105	163
Special Foreign Currency (P.L. 480) Grants[b]	—	372	176	64	—	1	290	—	325	262	—	150
B. Contracts												
Foreign Contracts	—	3,917	1,665	92	—	—	3,152	—	754	102	100	358
Foreign Components of Domestic Contracts	—	—	379	2	—	20	—	—	—	—	—	—
II. Scientist Exchanges												
A. Foreign Scientists in U.S.												
Visiting Fellows, Associates, Scientists	21	8,224	1,766	4,295	7	1,115	2,086	202	2,385	1,597	1,488	1,007
International Research Fellowships	—	—	—	—	—	—	—	—	—	—	—	—
Scholars-in-Residence	—	—	—	—	—	—	—	—	—	—	—	—
B. U.S. Scientists Abroad												
Senior International Fellowships	—	—	—	—	—	—	—	—	—	—	—	—
National Research Service Awards	—	88	172	33	—	8	25	—	25	24	—	—
Foreign Work Study Assignments	—	64	—	—	—	—	—	—	—	—	65	—
III. International Travel												
Contract/Grant Site Visits	1	74	10	1	—	—	32	1	10	4	7	7
Bilateral Agreement Related Travel	—	15	5	—	—	—	—	—	3	1	5	6
Other Bilateral Travel	—	48	2	—	1	—	7	—	—	—	—	10
Multilateral Organizations and Activities	3	15	—	—	—	—	—	—	1	—	—	—
International Meetings	19	161	45	46	16	43	86	10	69	46	36	22
Other International Travel	3	—	—	—	—	—	8	1	—	—	6	—
IV. Program Support												
Bilateral Exchanges	—	367	430	69	—	—	236	29	301	—	46	161
Other Program Support	100	102	332	98	200	20	119	—	144	23	97	38
TOTALS*	147	20,524	7,420	7,958	294	2,420	8,217	430	6,017	2,589	2,871	3,145

*Totals may not add because of rounding.
[a]The FIC serves as the administrative conduit for the core grant to the GMI.
[b]P.L. 480 funds are appropriated to the Office of the Assistant Secretary for Health, DHHS, and awarded and administered by the NIH.

Table I–1—Continued

TOTAL EXPENDITURES FOR NIH INTERNATIONAL PROGRAMS, BY ACTIVITY AND NIH COMPONENT, FY 1987
(in thousands of dollars)

	NIGMS	NINCDS	NCNR	FIC	CC	DCRT	DDR	DRS	TOTALS	Funds Expended in U.S.	Funds Expended Abroad
I. Research Awards											
A. Grants											
Foreign Research Grants	1,762	4,790	—	—	—	—	—	—	18,431		X
Cooperative Agreement Awards	—	—	—	—	—	—	—	—	3,719		X
Core Grant to Gorgas Memorial Institute[a]	—	—	—	1,934	—	—	—	—	1,934		X
Foreign Components of Domestic Grants	—	524	—	—	—	—	257	—	6,543		X
Special Foreign Currency (P.L. 480) Grants[b]	79	106	—	20	—	—	—	3	1,848		
B. Contracts											
Foreign Contracts	—	644	—	—	—	—	—	874	11,658		X
Foreign Components of Domestic Contracts	—	40	—	—	—	—	—	—	441		X
II. Scientist Exchanges											
A. Foreign Scientists in U.S.											
Visiting Fellows, Associates, Scientists	—	3,027	—	—	394	41	—	139	27,796	X	
International Research Fellowships	—	—	—	2,767	—	—	—	—	2,767	X	
Scholars-in-Residence	—	—	—	279	—	—	—	—	279	X	
B. U.S. Scientists Abroad											
Senior International Fellowships	—	—	—	921	—	—	—	—	921		X
National Research Service Awards	227	152	—	—	—	—	—	—	755		X
Foreign Work Study Assignments	—	—	—	—	—	—	—	—	129		X
III. International Travel											
Contract/Grant Site Visits	2	8	—	4	—	—	—	—	161	X	X
Bilateral Agreement Related Travel	—	—	—	6	—	—	—	—	41	X	X
Other Bilateral Travel	—	1	—	—	—	—	—	—	69	X	X
Multilateral Organizations and Activities	—	2	—	9	—	—	—	—	30	X	X
International Meetings	4	111	2	10	—	—	4	—	730	X	X
Other International Travel	—	2	—	—	—	—	—	—	20	X	X
IV. Program Support											
Bilateral Exchanges	—	2	—	584	—	—	—	3	2,228	X	X
Other Program Support	—	—	—	4,842	—	—	—	—	6,115	X	
TOTALS*	2,074	9,409	2	11,376	394	41	261	1,019	86,615	X	X

*Totals may not add because of rounding.
[a]The FIC serves as the administrative conduit for the core grant to the GMI.
[b]P.L. 480 funds are appropriated to the Office of the Assistant Secretary for Health, DHHS, and awarded and administered by the NIH.

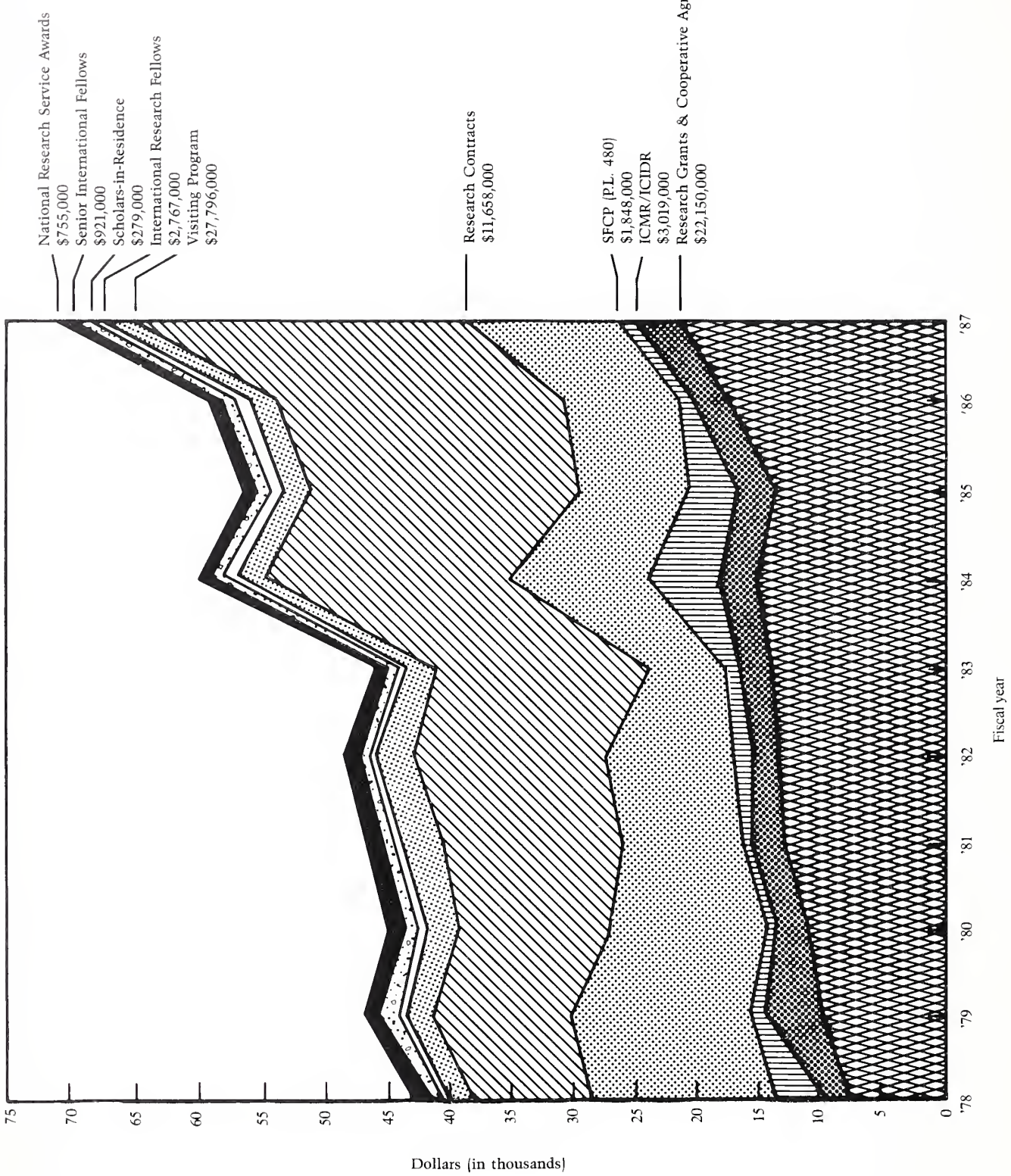


Figure I–2. NIH international research and research training awards, FY 1978–87

Almost 42 percent of the money devoted to international programs was actually spent in the United States. These programs include support for foreign scientists and Fogarty Scholars who study in the United States, for travel, and for bilateral exchanges to the United States of foreign scientists. Figure I–2 shows an overview of the funding for the various programs as it has changed over the past decade.

One source of funds for collaborative efforts, the Special Foreign Currency (P.L. 480) Program, is discussed in more detail in Chapter III under the Fogarty International Center (FIC) International Research and Awards program. Money is appropriated to the Office of the Assistant Secretary for Health, Department of Health and Human Services (DHHS), and is reviewed and administered by the NIH. In most cases, this source of support is gradually being replaced by matching funds administered by joint boards established by the United States and the foreign country. The joint boards review and monitor individual projects of mutual interest.

International biomedical programs involving the NIH may be part of broad science and technology agreements or of more specific health agreements (see Table I–2). Bilateral agreements, which are links between U.S. and foreign governments, are usually established through the Department of State. These agreements have been valuable in reducing social and political barriers to scientific exchanges, in capitalizing on unique features of local environments and resources, and in fostering collaborative undertakings with shared technical and professional resources and shared costs. In 1987, the NIH participated in 63 bilateral agreements involving 34 countries. The most recent agreement was signed with an Austrian organization in FY 1987.

Table I–3 shows the FY 1987 expenditures for research and research training awards by country or area and type of award. One hundred sixty-two foreign grants and contracts totaling $13.8 million were awarded to scientists in Canada, followed by awards to scientists from Japan (343 projects for $6.3 million), Israel (123 projects for $5.6 miilion), United Kingdom (148 projects for $4.7 million), China (119 projects for $2.9 million), and Italy (138 projects for $2.8 million).

Because several NIH and other Public Health Service (PHS) components participate in agreements with a given country, the liaison function of the FIC contributes to smooth coordination of the complex relationships. The FIC also has been given lead agency responsibility for the PHS for nine countries: Belgium, France, Federal Republic of Germany, Hungary, Japan, Poland, Romania, Venezuela, and Yugoslavia. This designation means that the FIC coordinates all PHS initiatives and activities, reports all accomplishments under these agreements, and serves as the focal point in these matters for the PHS and the Department of State.

All components of the NIH work closely with multilateral organizations, especially the World Health Organization (WHO). The FIC coordinates NIH advice for DHHS and its representation to WHO concerning agenda, budget, and policy issues. International organizations, including WHO, the Pan American Health Organization, and the International Agency for Research on Cancer, were awarded about $5.1 million in grants, contracts, or cooperative agreements in FY 1987. More specific accomplishments in each of these programs are described throughout the report.

Table I–4 provides a detailed breakdown of NIH international research and research training awards since 1947 (excluding travel and program support). Although training grants have been virtually eliminated, other programs, such as Fogarty Scholars-in-Residence and Senior International Fellowship Programs, have gained in importance. Over the years, Visiting Program support and research grants to foreign scientists have grown to a greater extent than other types of international activities, and the number of Guest Researchers has shown a steady increase.

Highlights of Recent Scientific Activities

National Cancer Institute

NCI participated in nine bilateral agreements on cooperative cancer research in FY 1987, emphasizing mutual contributions in collaborative ventures. The agreements were with the following countries: China, Egypt, France, Federal Republic of Germany, Hungary, Italy, Japan, Poland, and U.S.S.R.

The NCI European collaborative program continued to be highly successful in providing a regular flow of new compounds into the anticancer screen and an increasing number of new drugs for Phase I and II clinical evaluations. Approximately 2,000 new compounds have been acquired by the NCI Liaison Office in Brussels, Belgium, and screened at the Institute Jules Bordet under NCI contract. This represents a significant part of the total number of compounds put into the NCI screen.

In U.S.-China collaborative work, cancer epidemiology has been given the highest priority. The

Table I–2

INTERNATIONAL AGREEMENTS INVOLVING THE NIH

Country	Science and Technology	Health	NIH	No. of Agreements
Argentina	1972			1
Australia	1968			1
Austria			1987 NIH–FWF	1
Belgium			1984 NIH–FNRS	1
Brazil	1971		1977 NIH–PAHO	2
Bulgaria			1986 NIH–BMA	1
Canada			1970 NLM–CIST	1
China	1979	1979	1983 NIH–CAS	4
			1983 NINCDS–SBRI	
Colombia			1981 NLM–PAFMC	1
Czechoslovakia	1986			1
Egypt	1975	1975		2
Finland		1982	1982 NIEHS–FIOH	2
France			1984 NIH–INSERM	3
			1979 NIH–CNRS	
			1974 NLM–INSERM	
Germany, Fed. Rep.		1976	1974 NLM–DIMDI	3
			1981 NCI–MORT	
Greece	1980		1986 NIH–IMBB	2
Hungary	1977		1981 NCI–NIO	2
India	1974		1986 NIH–CSIR	2
Israel	1972	1980		2
Italy	1967	1977	1978 NLM–ISS	3
Japan	1980	1965	1976 NEI–JSPS	6
			1974 NLM–JICST	
			1973 NCI–JSPS	
			1984 NIA–TMIG	
Kenya[a]	1980			1
Korea	1976			1
Kuwait		1981	1981 NLM–MPH	2
Mexico	1972		1976 NLM–MOH	3
			1981 NIH–CINVESTAV	
Nigeria[a]	1980	1981		2
Pakistan	1982			1
Poland	1972	1973	1976 NCI–IO	3
Romania	1974			1
South Africa			1976 NLM–MRC	1
Spain	1976			1
Sri Lanka[a]	1984			1
Sweden			1974 NLM–SMRC	1
Switzerland			1980 NLM–SAMS	1
Thailand[a]	1984			1
United Kingdom			1974 NLM–BL	1
U.S.S.R.	1972	1972	1974 NHLBI–NRCC	3
Yugoslavia	1973			1
Zimbabwe[a]	1980			1
Taiwan	1980		1983 NIH–NSC	2
TOTALS: 39	26	11	32	69

[a]Agreements in force but inactive in FY 1987.

Chinese Academy of Medical Sciences is conducting experiments to evaluate the relationship between vitamin-mineral supplements and the prevention of esophageal cancer. Epidemiologic studies neared completion this year to identify environmental determinants of esophagus, lung, and stomach cancers and choriocarcinoma in four areas of China at high risk for these malignancies.

National Eye Institute

U.S.-China ophthalmic cooperation is under way, through a research agreement between NEI and

Zhongshan Medical College's Ophthalmic Center in China. An exchange of scientists at the institutions has begun, plus joint workshops and conferences. Collaborative research protocols have been developed, some of which are ready to be implemented.

Cataract is a leading cause of blindness in the world, causing severe visual loss in about 17 million people. NEI is sponsoring case-control studies in India, Italy, and the United States to determine personal and environmental risk factors—such as diet, systemic disease history, and exposure to sunlight and drugs—in hopes of learning how to prevent, or at least delay, the onset of age-related cataract.

In an attempt to restore effective eyesight through cataract operations, NEI collaborated with the Pan American Association of Ophthalmology and Helen Keller International in two demonstration projects. The projects, in Peru and Brazil, were designed to create zones free of operable cataract blindness. Deterrents to achieving the goal are being identified, and the lessons learned evaluated for their applicability throughout Latin America and other parts of the world.

National Heart, Lung, and Blood Institute

New information developed in epidemiologic studies with China and Japan raise important scientific questions about the overall process and predictors of cardiovascular disease. In China, these studies compared the trends and rates of cardiovascular disease and risk factors. For both Chinese men and women, workers' and farmers' mean blood pressure and prevalence rate of hypertension were significantly lower in the South than in the North; the mean serum total cholesterol for each also was lower in the South than in the North. Cholesterol levels of all Chinese populations were significantly lower than levels in U.S. populations studied, but the serum HDL-cholesterol levels were higher for Chinese men than U.S. men.

Cooperative U.S.-Japanese studies focus on hypertension and atherosclerosis. Both countries share a high prevalence of hypertension, but in Japan, stroke is the more common outcome, whereas in the United States, heart attack is more usual. Atherosclerosis is being measured in pathological specimens collected in both countries. The prevalence of atherosclerotic lesions in the coronary artery and abdominal aorta of a population studied in the United States was three times higher than in the corresponding Japanese population. Joint analyses show that although the Japanese diet is becoming more Western and presumably more atherogenic, ischemic heart disease rates are declining in Japan. This raises fundamental questions that scientists hope to address in future cooperative efforts.

Joint research activities under way with France and the Federal Republic of Germany include studies on the pulmonary aspects of acquired immunodeficiency syndrome (AIDS).

National Institute of Allergy and Infectious Diseases

NIAID is the lead institute in AIDS research at the NIH. In FY 1987, NIAID began the International Collaboration in AIDS Research (ICAR) Program, designed to support U.S.-based research institutions in studies with foreign counterparts. Grant applications are currently under review. Research areas are very broad and flexible; no restrictions are placed on the geographic location of the foreign collaborator.

NIAID-supported investigators from the Cornell Medical College entered the third year of a 5–year project to document the natural history of the human immunodeficiency virus (HIV) infection in Haiti. To date, the rate of progression to clinical AIDS among seropositive sexual partners has been 1 percent per month, more than double the rates observed in prospective studies carried out in the United States. Diarrhea, wasting, and "malignant AIDS pruritus," an intense, itchy skin condition, are much more common in Haiti than in the United States, yet, the prevalence of Kaposi's sarcoma is lower than in the United States and is decreasing.

NIAID-supported research in diarrheal diseases, including cholera, continued in FY 1987. The NIAID-supported Center for Vaccine Studies at the University of Maryland participated in studies in Bangladesh that showed that three doses of a killed cholera vaccine given orally provided 85 percent protection for at least 6 months against naturally acquired cholera (*Vibrio cholerae*).

National Institute of Arthritis and Musculoskeletal and Skin Diseases

In 1987, significant progress was made in two areas of research, Lyme borreliosis and juvenile arthritis, that are being studied through the U.S.-U.S.S.R. Cooperative Program in Arthritis. Arrangements exist for continued collaborative studies in 1987–89, including the epidemiology of rheumatic diseases.

National Institute of Child Health and Human Development

A scientist from Israel is trying to determine at the molecular level how chromosome 21 produces Down syndrome, the most common genetic birth defect

Table I–3

NIH INTERNATIONAL RESEARCH AND RESEARCH TRAINING AWARDS
BY COUNTRY/AREA AND MECHANISM, FY 1987
(in thousands of dollars)

Country/Area	Total		Research Grants		Cooperative Agreements		ICIDR		SFCP (P.L. 480)	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Algeria	1	21	—	—	—	—	—	—	—	—
Argentina	33	753	3	124	—	—	—	—	—	—
Australia	58	2,406	14	1,262	—	—	—	—	—	—
Austria	10	181	—	—	—	—	—	—	—	—
Bahamas	1	18	—	—	—	—	—	—	—	—
Bangladesh	2	32	—	—	—	—	—	—	—	—
Barbados	1	33	—	—	—	—	—	—	—	—
Belgium	25	1,097	4	239	—	—	—	—	—	—
Bolivia	1	27	—	—	—	—	—	—	—	—
Brazil	24	1,264	1	45	—	—	2	815	—	—
Bulgaria	1	24	—	—	—	—	—	—	—	—
Burma	—	—	—	—	—	—	—	—	—	—
Canada	162	13,821	80	9,302	21	1,498	—	—	—	—
Chile	15	361	1	84	—	—	—	—	—	—
China	119	2,942	3	127	—	—	—	—	—	—
Colombia	9	1,031	—	—	—	—	2	860	—	—
Costa Rica	1	26	—	—	—	—	—	—	—	—
Czechoslovakia	3	42	—	—	—	—	—	—	—	—
Denmark	12	477	—	—	—	—	—	—	—	—
Dominican Republic	1	28	—	—	—	—	—	—	—	—
Egypt	2	481	—	—	—	—	—	—	—	—
Ethiopia	3	334	—	—	—	—	1	285	—	—
Finland	20	932	3	253	—	—	—	—	—	—
France	57	1,013	1	81	—	—	—	—	—	—
Germany, Fed. Rep.	52	841	1	71	—	—	—	—	—	—
Ghana	2	49	—	—	—	—	—	—	—	—
Greece	13	282	—	—	—	—	—	—	—	—
Hong Kong	3	43	—	—	—	—	—	—	—	—
Hungary	20	339	—	—	—	—	—	—	—	—
Iceland	1	38	—	—	—	—	—	—	—	—
India	135	2,259	—	—	—	—	—	—	31	351
Indonesia	1	169	—	—	—	—	1	169	—	—
Iran	1	5	—	—	—	—	—	—	—	—
Ireland	10	263	1	69	—	—	—	—	—	—
Israel	123	5,557	46	3,470	—	—	—	—	—	—
Italy	138	2,772	3	97	1	193	—	—	—	—
Jamaica	3	384	—	—	—	—	—	—	—	—
Japan	343	6,318	1	57	—	—	—	—	—	—
Jordan	1	18	—	—	—	—	—	—	—	—
Kenya	—	—	—	—	—	—	—	—	—	—
Korea	30	512	—	—	—	—	—	—	—	—

Lebanon	2	33	—	—	—	—	—	—	—	—
Luxembourg	1	18	—	—	—	—	—	—	—	—
Malaysia	—	—	—	—	—	—	—	—	—	—
Mali	—	—	—	—	—	—	—	—	—	—
Malta	1	25	—	—	—	—	—	—	—	—
Mauritania	—	—	—	—	—	—	—	—	—	—
Mexico	8	208	1	49	—	—	—	—	—	—
Netherlands	24	552	1	76	2	21	—	—	—	—
New Zealand	15	506	3	233	—	—	—	—	—	—
Nigeria	7	180	—	—	—	—	—	—	—	—
Norway	6	379	—	—	—	—	—	—	—	—
Pakistan	6	1,059	—	—	—	—	—	—	5	1,034
Peru	3	468	—	—	—	—	1	439	—	—
Philippines	3	113	—	—	—	—	—	—	—	—
Poland	41	939	—	—	—	—	—	—	2	118
Portugal	5	119	1	63	—	—	—	—	—	—
Romania	2	59	1	58	—	—	—	—	—	—
Saudi Arabia	2	15	—	—	—	—	—	—	—	—
Senegal	1	27	—	—	—	—	—	—	—	—
Sierra Leone	1	10	—	—	—	—	—	—	—	—
Singapore	1	5	—	—	—	—	—	—	—	—
South Africa	7	183	—	—	—	—	—	—	—	—
Spain	39	644	1	28	—	—	—	—	—	—
Sudan	2	380	—	—	—	—	1	355	—	—
Sweden	33	2,691	15	1,046	—	—	—	—	—	—
Switzerland	30	670	3	93	—	—	—	—	—	—
Tanzania	1	117	—	—	—	—	—	—	—	—
Thailand	6	160	1	39	—	—	—	—	—	—
Tunisia	2	29	—	—	—	—	—	—	—	—
Turkey	2	41	—	—	—	—	—	—	—	—
Uganda	1	3	—	—	—	—	—	—	—	—
United Kingdom	148	4,727	19	1,240	1	201	—	—	—	—
United States	108	3,056	—	—	—	—	—	—	—	—
Uruguay	2	55	—	—	—	—	—	—	—	—
U.S.S.R.	—	—	—	—	—	—	—	—	—	—
Venezuela	5	237	—	—	—	—	1	96	—	—
Vietnam	1	6	—	—	—	—	—	—	—	—
Yugoslavia	36	564	1	51	—	—	—	—	25	345
Zaire	1	31	—	—	—	—	—	—	—	—
Taiwan	13	311	—	—	—	—	—	—	—	—
International Organizations										
EORTC	2	434	—	—	1	274	—	—	—	—
IARC	4	888	2	138	2	750	—	—	—	—
IUAC	3	274	2	37	—	—	—	—	—	—
PAHO	4	2,373	—	—	—	—	—	—	—	—
WHO	4	1,133	—	—	1	683	—	—	—	—
TOTALS*	2,020	70,914[b]	213	18,431	29	3,719	9	3,019	63	1,848

*Totals may not add because of rounding.

[a]Numbers in parentheses are *not* included in totals; Guest Researchers are supported by home institutions, foundations, and other sources.

[b]Does not include Scholars-in-Residence awards.

Table I–3—Continued

NIH INTERNATIONAL RESEARCH AND RESEARCH TRAINING AWARDS
BY COUNTRY/AREA AND MECHANISM, FY 1987
(in thousands of dollars)

Country/Area	Research Contracts		Visiting Program		International Research Fellows		Guest Researchers[a]	Senior International Fellows		National Research Service Awards	
	Number	Amount	Number	Amount	Number	Amount	(Number)	Number	Amount	Number	Amount
Algeria	—	—	1	21	—	—	(1)	—	—	—	—
Argentina	—	—	26	525	4	104	(8)	—	—	—	—
Australia	2	46	32	524	2	50	(6)	3	26	5	108
Austria	—	—	9	147	—	—	(9)	1	34	—	—
Bahamas	—	—	1	18	—	—	—	—	—	—	—
Bangladesh	—	—	2	32	—	—	—	—	—	—	—
Barbados	—	—	1	33	—	—	—	—	—	—	—
Belgium	2	484	14	248	4	107	(5)	1	19	—	—
Bolivia	—	—	—	—	1	27	—	—	—	—	—
Brazil	—	—	16	285	4	109	(4)	1	10	—	—
Bulgaria	—	—	1	24	—	—	(2)	—	—	—	—
Burma	—	—	—	—	—	—	(1)	—	—	—	—
Canada	13	1,992	40	870	3	71	(29)	—	—	5	88
Chile	1	5	13	272	—	—	(4)	—	—	—	—
China	3	768	109	1,950	3	87	(43)	1	10	—	—
Colombia	—	—	4	88	3	83	(1)	—	—	—	—
Costa Rica	—	—	1	26	—	—	—	—	—	—	—
Czechoslovakia	—	—	3	42	—	—	—	—	—	—	—
Denmark	2	285	7	133	2	50	(7)	1	9	—	—
Dominican Republic	—	—	—	—	1	28	—	—	—	—	—
Egypt	1	478	1	3	—	—	(1)	—	—	—	—
Ethiopia	—	—	1	19	1	30	(1)	—	—	—	—
Finland	1	304	9	190	6	167	(7)	1	18	—	—
France	—	—	44	669	6	153	(25)	5	90	1	20
Germany, Fed. Rep.	—	—	44	663	—	—	(59)	1	5	6	102
Ghana	1	45	1	4	—	—	(1)	—	—	—	—
Greece	1	69	11	185	1	28	(9)	—	—	—	—
Hong Kong	—	—	3	43	—	—	(2)	—	—	—	—
Hungary	—	—	20	339	—	—	(4)	—	—	—	—
Iceland	—	—	1	38	—	—	—	—	—	—	—
India	—	—	101	1,815	2	58	(33)	1	35	—	—
Indonesia	—	—	—	—	—	—	(1)	—	—	—	—
Iran	—	—	1	5	—	—	—	—	—	—	—
Ireland	—	—	6	113	3	81	(3)	—	—	—	—
Israel	4	683	69	1,301	3	78	(24)	—	—	1	25
Italy	2	143	129	2,257	3	82	(65)	—	—	—	—
Jamaica	1	311	2	73	—	—	—	—	—	—	—
Japan	1	29	334	6,049	5	136	(68)	1	18	1	29
Jordan	—	—	1	18	—	—	—	—	—	—	—
Kenya	—	—	—	—	—	—	(1)	—	—	—	—
Korea	—	—	27	430	3	82	(13)	—	—	—	—

Lebanon	—	—	1	6	1	27	—	—	—	—	—
Luxembourg	—	—	1	18	—	—	—	—	—	—	—
Malaysia	—	—	—	—	—	—	(1)	—	—	—	—
Mali	—	—	—	—	—	—	(1)	—	—	—	—
Malta	—	—	1	25	—	—	—	—	—	—	—
Mauritania	—	—	—	—	—	—	(1)	—	—	—	—
Mexico	—	—	5	113	2	46	(3)	—	—	—	—
Netherlands	—	—	17	288	—	—	(10)	3	42	1	25
New Zealand	—	—	8	185	3	82	(5)	1	6	—	—
Nigeria	—	—	3	67	4	113	—	—	—	—	—
Norway	1	250	3	71	2	58	(2)	—	—	—	—
Pakistan	—	—	1	25	—	—	(1)	—	—	—	—
Peru	—	—	2	29	—	—	—	—	—	—	—
Philippines	—	—	3	113	—	—	(2)	—	—	—	—
Poland	—	—	34	685	5	136	(1)	—	—	—	—
Portugal	—	—	4	56	—	—	(1)	—	—	—	—
Romania	—	—	1	1	—	—	—	—	—	—	—
Saudi Arabia	—	—	2	15	—	—	—	—	—	—	—
Senegal	—	—	—	—	1	27	—	—	—	—	—
Sierra Leone	—	—	1	10	—	—	—	—	—	—	—
Singapore	—	—	1	5	—	—	—	—	—	—	—
South Africa	—	—	7	183	—	—	(1)	—	—	—	—
Spain	—	—	34	507	4	109	(19)	—	—	—	—
Sudan	—	—	1	25	—	—	—	—	—	—	—
Sweden	5	1,339	7	162	5	135	(4)	1	9	—	—
Switzerland	—	—	19	405	1	28	(7)	3	60	4	84
Tanzania	1	117	—	—	—	—	—	—	—	—	—
Thailand	—	—	2	42	3	79	—	—	—	—	—
Tunisia	—	—	2	29	—	—	—	—	—	—	—
Turkey	—	—	2	41	—	—	(1)	—	—	—	—
Uganda	—	—	1	3	—	—	(1)	—	—	—	—
United Kingdom	4	700	88	1,748	3	74	(13)	21	494	12	270
United States	—	—	108	3,056	—	—	(20)	—	—	—	—
Uruguay	—	—	1	26	1	29	(1)	—	—	—	—
U.S.S.R.	—	—	—	—	—	—	(1)	—	—	—	—
Venezuela	—	—	3	113	1	28	—	—	—	—	—
Vietnam	—	—	1	6	—	—	—	—	—	—	—
Yugoslavia	—	—	8	114	2	54	(3)	—	—	—	—
Zaire	—	—	1	31	—	—	—	—	—	—	—
Taiwan	—	—	7	143	5	134	(2)	1	34	—	—
International Organizations											
EORTC	1	160	—	—	—	—	—	—	—	—	—
IARC	—	—	—	—	—	—	—	—	—	—	—
IUAC	1	237	—	—	—	—	—	—	—	—	—
PAHO	4	2,373	—	—	—	—	—	—	—	—	—
WHO	3	450	—	—	—	—	—	—	—	—	—
TOTALS*	55	11,658	1,465	27,796	103	2,767	(538)	47	921	36	755

*Totals may not add because of rounding.

[a]Numbers in parentheses are not included in totals; Guest Researchers are supported by home institutions, foundations, and other sources.

Table I–4

NIH INTERNATIONAL RESEARCH AND RESEARCH TRAINING AWARDS, FY 1947–87[a]

(in thousands of dollars)

Fiscal Year	Total		Research Grants		ICMR/ICIDR[b]		SFCP (P.L. 480)		Training Grants		Research Contracts	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount
1947	19	179	5	130	—	—	—	—	—	—	—	—
1948	37	346	11	253	—	—	—	—	—	—	—	—
1949	79	347	16	130	—	—	—	—	—	—	—	—
1950	68	391	20	219	—	—	—	—	—	—	—	—
1951	83	412	28	210	—	—	—	—	—	—	—	—
1952	85	495	22	257	—	—	—	—	—	—	—	—
1953	79	495	24	245	—	—	—	—	—	—	—	—
1954	88	497	15	145	—	—	—	—	—	—	—	—
1955	88	470	14	111	—	—	—	—	—	—	—	—
1956	116	683	18	190	—	—	—	—	—	—	—	—
1957	224	1,808	61	824	—	—	—	—	1	13	—	—
1958	318	2,777	92	1,307	—	—	—	—	1	17	—	—
1959	495	5,425	170	2,997	—	—	—	—	2	30	—	—
1960	749	8,492	307	5,249	—	—	—	—	3	39	3	90
1961	1,064	12,692	563	8,999	—	—	—	—	7	251	2	118
1962	1,416	22,770	811	13,410	5	2,093	20	2,765	13	380	8	181
1963	1,707	24,067	981	14,956	7	2,093	16	1,517	16	536	5	182
1964	1,645	25,590	932	13,759	6	2,484	19	3,328	17	544	13	429
1965	1,540	23,514	801	11,467	6	2,491	25	3,026	22	615	22	867
1966	1,494	21,653	718	10,010	5	2,423	22	2,182	18	559	29	901
1967	1,218	20,068	624	8,509	5	2,360	27	3,559	15	506	27	1,037
1968	1,066	20,525	480	6,424	5	2,360	42	5,459	16	449	35	1,325
1969	950	19,985	325	4,481	5	2,294	44	7,312	11	187	32	1,369
1970	756	15,267	170	2,968	4	2,070	39	4,503	4	6	34	1,805
1971	736	21,844	120	2,489	5	2,285	79	10,149	—	—	41	2,319
1972	850	19,762	113	2,449	4	2,399	24	2,894	—	—	65	5,337
1973	782	19,874	116	2,905	4	2,244	21	2,706	—	—	86	6,508
1974	861	23,020	119	3,360	4	2,360	13	1,544	—	—	105	8,381
1975	1,002	31,867	130	3,917	4	2,411	24	3,257	—	—	120	13,790
1976	1,235	34,457	138	5,128	4	2,400	18	2,934	—	—	134	12,525
1977	1,304	40,719	149	6,532	4	2,400	25	4,484	—	—	135	15,173
1978	1,404	42,829	162	7,502	4	2,117	16	4,199	—	—	139	15,107
1979	1,452	47,333	191	10,042	13	4,699	9	1,298	—	—	117	14,759
1980	1,485	45,179	206	11,139	10	2,756	9	612	—	—	93	12,932
1981	1,548	46,622	237	13,223	10	2,585	20	911	—	—	61	9,672
1982	1,532	48,598	212[c]	13,336[c]	8	2,384	19	1,424	—	—	53	10,608
1983	1,595	46,023	214[c]	14,079[c]	9	2,741	14	945	—	—	37	6,597
1984	1,644	60,227	191[c]	15,708[c]	9	2,870	39	6,128	—	—	43	11,094
1985	1,827	59,047	220[c]	15,466[c]	10	2,998	47	4,560	—	—	55	8,767
1986	1,900	58,385	219[c]	16,723[c]	9	2,933	29	998	—	—	63	9,276
1987	2,026	71,193	242[c]	22,150[c]	9	3,019	63	1,848	—	—	55	11,658

[a]Table I–4 includes only those categories in Table I–1 that constitute research and research training awards.

[b]International Centers for Medical Research (ICMRs) existed from FY 1962 through FY 1979, when program changes resulted in the phasing out of ICMRs and the initiation of grants under the International Collaboration in Infectious Diseases Research (ICIDR) Program.

[c]Includes cooperative agreement awards.

Table I–4—Continued

NIH INTERNATIONAL RESEARCH AND RESEARCH TRAINING AWARDS, FY 1947–87[a]
(in thousands of dollars)

Fiscal Year	Visiting Program		International Research Fellows		Scholars-in-Residence		Guest Researchers	Senior International Fellows		National Research Service Awards	
	Number	Amount	Number	Amount	Number	Amount	Number	Number	Amount	Number	Amount
1947	—	—	13	48	—	—	—	—	—	1	1
1948	—	—	13	48	—	—	—	—	—	1	1
1949	—	—	55	183	—	—	—	—	—	8	29
1950	1	—	36	135	—	—	—	—	—	11	37
1951	5	29	37	127	—	—	—	—	—	13	47
1952	7	42	36	119	—	—	—	—	—	20	78
1953	6	42	13	41	—	—	—	—	—	36	168
1954	17	115	2	1	—	—	—	—	—	54	236
1955	26	165	—	—	—	—	—	—	—	48	194
1956	42	270	—	—	—	—	—	—	—	56	224
1957	76	518	—	—	—	—	—	—	—	86	453
1958	110	785	16	102	—	—	—	—	—	99	566
1959	128	1,097	67	467	—	—	—	—	—	128	834
1960	138	1,035	68	501	—	—	—	—	—	230	1,577
1961	149	869	—	—	—	—	—	—	—	251	1,780
1962	190	1,052	90	681	—	—	—	—	—	279	2,207
1963	200	1,203	172	1,199	310	—	—	—	—	—	2,381
1964	179	1,434	183	1,199	—	—	—	—	—	296	2,413
1965	156	1,172	166	1,199	—	—	—	—	—	342	2,678
1966	139	1,194	166	1,197	—	—	—	—	—	397	3,188
1967	129	1,157	176	1,200	—	—	(87)	—	—	211	1,740
1968	149	1,405	151	1,379	—	—	(95)	—	—	188	1,724
1969	138	1,299	168	1,409	5	130	(93)	—	—	222	1,504
1970	178	1,628	137	1,027	5	119	(53)	—	—	185	1,101
1971	188	2,070	130	1,077	6	141	(100)	—	—	167	1,314
1972	259	3,108	163	1,588	8	182	(118)	—	—	214	1,806
1973	290	3,763	110	777	12	228	(134)	—	—	143	742
1974	351	4,506	127	1,489	13	219	(145)	—	—	129	1,162
1975	494	5,946	107	1,370	8	163	(157)	—	—	115	1,014
1976	676	7,948	137	1,605	8	150	(180)	42	717	75	1,050
1977	740	8,404	126	1,636	16	362	(159)	50	906	59	823
1978	804	9,469	128	2,094	12	253	(205)	64	1,203	75	1,065
1979	830	11,159	134	2,413	11	272	(229)	75	1,680	72	1,009
1980	909	12,445	132	2,263	20	715	(266)	52	1,227	54	1,090
1981	976	14,568	136	3,450	18	456	(355)	32	673	58	1,084
1982	979	15,722	153	3,061	20	485	(381)	29	593	59	985
1983	1,128	16,953	101	2,689	8	357	(390)	41	926	43	756
1984	1,176	19,654	87	2,357	12	565	(396)	53	1,240	34	611
1985	1,288	21,882	104	2,794	10	402	(479)	45	1,165	48	1,013
1986	1,391	23,659	101	2,727	14	446	(551)	40	868	34	755
1987	1,465	27,796	103	2,767	6	279	(538)	47	921	36	755

[a]Table I–4 includes only those categories in Table I–1 that constitute research and research training awards.
[b]International Centers for Medical Research (ICMRs) existed from FY 1962 through FY 1979, when program changes resulted in the phasing out of ICMRs and the initiation of grants under the International Collaboration in Infectious Diseases Research (ICIDR) Program.
[c]Includes cooperative agreement awards.

associated with mental retardation. The findings should define the biochemical pathways affected in the syndrome and may pave the way for therapies to prevent some of the symptoms of Down syndrome.

A multinational study is under way to acquire data about perinatal and infant mortality rates in other developed countries to enable comparisons with data from the United States.

National Institute of Dental Research

A new understanding of basement membranes—which surround all blood vessels, glands, nerves, and muscles and hold the cells of a tissue in place—has resulted from work by scientists at the National Institute of Dental Research. Tumor cells must invade basement membranes in order to metastasize. NIDR researchers, in collaboration with visiting investigators, have pinpointed the structure and role of many of the proteins that constitute basement membranes. They discovered that a synthetic mimic of one of these proteins hampers the spread of tumors in mice lungs, apparently by inhibiting the binding of tumor cells to basement membranes. A research team also developed a laboratory test that measures the invasiveness of tumor cells and can be used to test the effectiveness of anticancer drugs.

National Institute of Diabetes and Digestive and Kidney Diseases

Several U.S.-Japanese epidemiologic studies of diabetes mellitus have produced data on this disease's incidence, prevalence, complications, and associated factors. The study results suggest an inherent predisposition to impaired glucose tolerance and arteriosclerotic heart disease that is affected by environmental variables such as diet, health habits, psychosocial stress, and cultural factors as well as age, body fat, glycemia, plasma lipids, and hormone levels.

Two grants for identifying genes for specific serious chronic diseases have been partially successful. British researchers found the locus for adult polycystic kidney disease (APKD) on the short arm of chromosome 16. APKD causes about 10 percent of end-stage renal disease. U.S., British, and Canadian scientists studying cystic fibrosis (CF) narrowed the location of the CF gene to the middle third of the long arm of chromosome 7, a region of about 1 million DNA base pairs. In affected families, this makes it possible to predict children affected with CF, but it is not specific enough for diagnosis of asymptomatic carriers in the general population.

National Institute of Neurological and Communicative Disorders and Stroke

NINCDS undertook an initiative against one of the world's top killers—stroke. Through a grant awarded to a Canadian medical center, the Institute has begun a collaborative clinical trial to determine whether a commonly performed operation to prevent stroke, carotid endarterectomy, actually works. The study will weigh the benefits and risks of the operation and produce a guideline to help physicians decide which patients are most likely to benefit from the procedure.

Work to combat Huntington's disease (HD)—an inherited disorder of midlife onset in which premature brain cell death causes progressive loss of mental and motor skills—led to several important advances by American and Venezuelan scientists. This year, they discovered a second marker gene, whose location should speed the mapping and cloning of the HD gene itself. They also verified the first marker gene's persistent inheritance along with the HD gene in all families tested.

More knowledge about Alzheimer's disease and Down syndrome resulted from collaborative efforts between U.S. and French scientists at the Laboratoire de Biochimie Génétique in Paris. The scientists found that patients with nonfamilial Alzheimer's disease and some types of Down syndrome have an extra copy of the gene involved in making amyloid, a substance found in high concentrations in the brains of Alzheimer's patients.

NINCDS-supported scientists in Australia are working to create an implantable device that would allow the profoundly deaf to hear. The multiple-channel cochlear prosthesis uses a tiny electronic stimulator and receiver to create hearing sensations. This year scientists at the University of Melbourne in Victoria implanted the device in deaf patients and are testing to see what types of hearing sensations occur.

National Institute on Aging

Results from a U.S.-Swedish collaborative study indicate that brain tissue transplants can reverse learning deficits in severely impaired, aged animals.

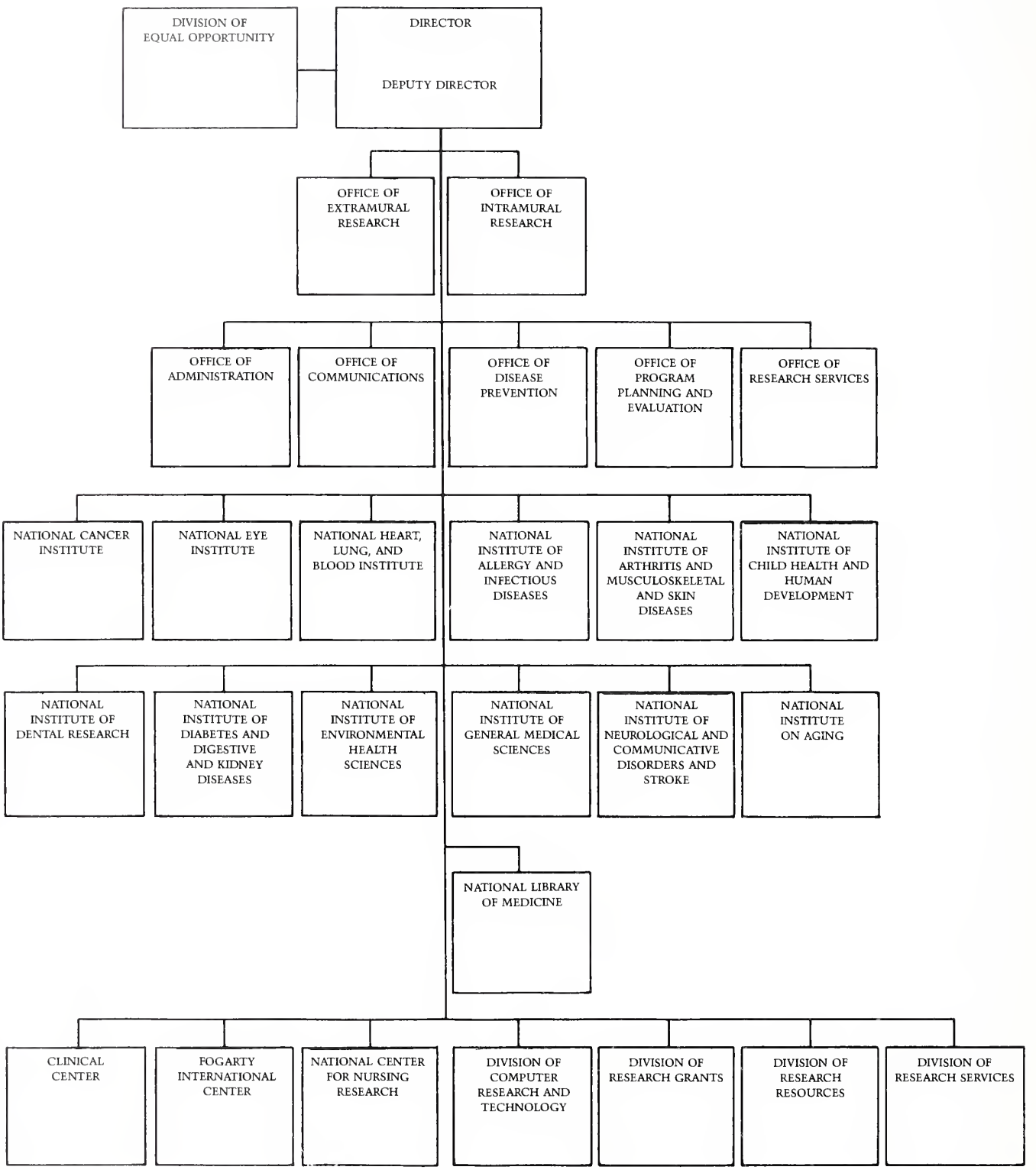
An international set of quantitative standards for the pathological diagnosis of Alzheimer's disease was produced this year as a result of an NIA grant to a researcher at the University of Western Ontario. Although these standards will require further testing in other patient series, they are expected to be a major contribution to the development of research for national and cross-cultural comparative studies.

National Library of Medicine

NLM continued its bilateral cooperative MEDLARS agreements with institutions in 15 countries. Representatives from India visited NLM in preparation for setting up a MEDLARS Center in New Delhi.

NLM held an invitational workshop, co-sponsored by other NIH components, in which 45 participants from 22 developing countries exchanged viewpoints on international collaboration on the application of medical informatics. One consensus was that the rate of computer use in medicine in developing countries was not progressing at nearly the rate as in developed nations. Unless international collaboration exists, the gap between the developed and developing countries will not narrow.

Figure I–3. Components of the National Institutes of Health


DIVISION OF EQUAL OPPORTUNITY
DIRECTOR
DEPUTY DIRECTOR
OFFICE OF EXTRAMURAL RESEARCH
OFFICE OF INTRAMURAL RESEARCH
OFFICE OF ADMINISTRATION
OFFICE OF COMMUNICATIONS
OFFICE OF DISEASE PREVENTION
OFFICE OF PROGRAM PLANNING AND EVALUATION
OFFICE OF RESEARCH SERVICES
NATIONAL CANCER INSTITUTE
NATIONAL EYE INSTITUTE
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES
NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
NATIONAL INSTITUTE OF DENTAL RESEARCH
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
NATIONAL INSTITUTE ON AGING
NATIONAL LIBRARY OF MEDICINE
CLINICAL CENTER
FOGARTY INTERNATIONAL CENTER
NATIONAL CENTER FOR NURSING RESEARCH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH RESOURCES
DIVISION OF RESEARCH SERVICES

Chapter II
Office of the Director, National Institutes of Health

Introduction

The Director of the NIH manages the organization's domestic and international responsibilities to improve human health through the conduct and support of biomedical research. The Director gives overall policy and management leadership to the NIH and maintains close liaison with the Assistant Secretary for Health, DHHS, in matters relating to medical research training, education and training in the health professions, manpower resources, and biomedical communications. The Director also works closely with other DHHS constituents for effective program coordination.

On matters of worldwide concern, the Director participates in international conferences and in meetings with officials of foreign governments. Such meetings establish initial contacts that often evolve into long-term relationships with scientists and organizations in other countries.

The Office of the Director, NIH, comprises a Deputy Director; Deputy Directors for Intramural Research and for Extramural Research; and Associate Directors for Administration, Clinical Care, Communications, Disease Prevention, Extramural Affairs, International Research, Intramural Affairs, Program Planning and Evaluation, and Research Services; the Director, Division of Equal Employment Opportunity; and the Assistant Director for Program Coordination.

The NIH Associate Director for International Research is responsible for coordinating and integrating the international aspects of biomedical and behavioral research of the NIH and serves as a major source of advice to the NIH Director on all matters related to international health. Throughout FY 1987, this position was held jointly by the Fogarty International Center (FIC) Director, and accomplishments and activities are reported in the chapter on the FIC.

NIH Centennial Events

The first 100 years of NIH history were celebrated with special Centennial events at home and abroad beginning in October 1986. Activities observing the hallmark year involved the President, Members of Congress, officials of DHHS and the Public Health Service (PHS), U.S. and foreign scientists, past and present NIH employees, and representatives from foreign countries, scientific groups, voluntary health organizations, medical institutions, private industry, and the public.

During the past century, the NIH has grown from a one-room laboratory in the attic of the Marine Health Service Hospital on Staten Island to one of the world's largest biomedical research institutions. The primary goal of the Centennial observance was to educate the public about health benefits resulting from biomedical research accomplishments of the last 100 years and about the roles that the NIH, academia, the private sector, and voluntary and professional organizations have played in these accomplishments. A second objective was to stimulate young peoples' interest in biomedical research careers so that progress will continue during the next 100 years.

Four Centennial events international in scope were held in the United States in FY 1987:

- May 11–14, NIH. An FIC Scholars-in-Residence Centennial symposium entitled "The Impact of Modern Biology on Health Research."
- May 26–28, NIH. An NIH-Pasteur symposium entitled "Impact of Molecular Biology on Biomedical Research."
- June 8–9, NIH. The NIH hosted the annual meeting of the Standing Committee of the European Medical Research Councils (EMRC). The NIH pro-

gram focused on Centennial and scientific topics of current interest to EMRC member countries.

- September 25, Headquarters of the Pan American Health Organization (PAHO), Washington, D.C. The PAHO Directing Council passed a resolution acknowledging the Centennial; a panel presentation entitled "NIH-PAHO Cooperation in the Health Sciences: Yesterday, Today, and Tomorrow" followed.

Eight Centennial events were hosted by foreign countries in FY 1987:

- March 21, Basel, Switzerland. A symposium on "The Platelet, a Model for Pathophysiological Research," dedicated to the 100th anniversary of the NIH and the 10th anniversary of the Department of Research of the University Clinics, Basel.
- June 29–30, Kyoto, Japan. A scientific and social event hosted by the NIH Alumni Association in Japan to commemorate the NIH Centennial and NIH-Japan cooperation in biomedical research.
- July 15–16, Wellington, New Zealand. A joint celebration of the NIH Centennial and the Medical Research Council of New Zealand's 50th anniversary.
- July 27, Zagreb, Yugoslavia. Ceremony to dedicate the Clinical Hospital of the Center of Medical Sciences, Zagreb.
- July 30–31, Munich, Federal Republic of Germany. A symposium sponsored by the Gesellschaft für Strahlen-und-Umweltforschung and the Deans of the Faculties of Medicine from the Ludwig-Maximillian Universität München and the Technische Universität München.
- August 21–23, Mexico City, Mexico. A Centennial commemoration at the Instituto Nacionale de la Nutricion.
- September 17, Budapest, Hungary. A scientific session at Semmelweis Medical University to celebrate the NIH Centennial.
- September 22, Helsinki, Finland. A reception in honor of the NIH Centennial anniversary, at the University of Helsinki, hosted by the Finnish Nominating Committee for the FIC International Research Fellowship Program.

Other significant celebrations of the Centennial took place through the end of calendar year 1987.

During FY 1987, the NIH Director discussed biomedical research programs with the following dignitaries:

- Secretary of the National Health and Medical Research Council of Australia;
- Members of the Science and Technology Committee of the Japanese Diet;
- The Prime Minister and Minister of Health of Japan;
- Members of the British House of Lords;
- The Prime Minister of Sweden;
- The Swedish Minister of Health and Social Welfare;
- The President of the Italian National Research Council; and
- The President of the Bulgarian Medical Academy.

The NIH Deputy Directors held discussions with the Secretary of Health of India; the Italian Minister of the Environment; the Director, Indian Council of Medical Research; and the Director of the Japanese International Frontier Research Program.

European Medical Research Councils

The NIH participates as an observer at annual meetings of the standing committee of the European Medical Research Councils, which has 16 member states. Although the NIH is not a party to official actions taken by EMRC, NIH representatives participate freely in discussions of agenda items, and the NIH Director reports on NIH activities. In June 1987, the Director hosted the 27th EMRC meeting in Bethesda. Agenda items of interest to the NIH, or in which the NIH has been involved through participation on subgroup advisory committees, included:

- Advisory subgroup on toxicology;
- Advisory subgroup on human reproduction;
- Study group on mental illness research;
- Planning committee on technology assessment;
- European training program in brain and behavior research; and
- Gene therapy.

Pan American Health Organization

The Associate Director for International Research was a member of the U.S. delegation to the PAHO Executive Committee Meeting held in Washington, D.C., in June 1987, and also served as the U.S. del-

egate to the 32nd PAHO Directing Council meeting, held in Washington, D.C., in September 1987. He met with senior PAHO officials and senior members of health ministries from PAHO member countries to discuss policy, planning, and implementation of research programs related to NIH involvement in the region.

World Health Organization

The Associate Director for International Research served as an advisor to the U.S. delegation to the 40th World Health Assembly in Geneva in May 1987. The Under Secretary for Health and Human Services headed the delegation, and the Public Health Service Surgeon General served as Deputy Chief Delegate. In his role as NIH representative, the Associate Director met with senior World Health Organization (WHO) officials and senior members of health ministries from WHO member countries to discuss policy, planning, and implementation of research programs related to the global strategy of Health for All by the Year 2000; they also discussed matters related to NIH bilateral and multilateral activities.

Office of Intramural Research

The Deputy Director for Intramural Research handles scientific policy problems of the NIH components and is their representative in the overall council of the NIH.

Canada

As a member of a scientific review committee, the Deputy Director for Intramural Research in January 1987 participated in a site visit to survey the clinical and basic scientific research programs of the Institut de Recherches Cliniques de Montréal.

As a longstanding member of the Board of Directors of the Laurentian Hormone Conference, the Deputy Director attended the August 1987 conference in Montebello.

Italy

In June, the Deputy Director for Intramural Research attended a University of Naples meeting of the Scientific Council of the Centro di Endocrinologia e Oncologia Sperimentale del Consiglio Nazionale delle Ricerche, in his position as council chairman. He also participated in scientific discussions at the University of Rome.

Netherlands

As a member of the Commission on Life Sciences of the National Research Council, the Deputy Director attended the first meeting of COBIOTECH (International Scientific Committee for Biotechnology) held in Amsterdam in June 1987. It was organized by the Scientific Committee for Biotechnology of the International Council of Scientific Unions.

United Kingdom

In September, the Deputy Director for Intramural Research spoke on "Implications of New Biology" at the Oxford International Symposium 1987. He also visited the Medical Research Council in London.

Office of Extramural Research

The Deputy Director for Extramural Research has broad policy responsibilities for the extramural programs of the NIH. The office also coordinates those areas of science that overlap several components of the NIH.

In 1987, the office focused on acquired immunodeficiency syndrome (AIDS). By virtue of his expertise on antiviral drugs and AIDS, the Deputy Director for Extramural Research chaired the Third International Conference on AIDS in Washington, D.C., June 1–5. The conference was attended by 7,000 people representing 99 countries, including more than 900 from the news media. It was multidisciplinary in scope and brought together administrators, doctors, scientists, sociologists, ethicists, lawyers, educators, and the public. International experts shared their findings on the natural history of the disease, epidemiology, molecular biology, immunology, clinical studies, ethics, and public health education.

The AIDS conference resulted in the formation of an International AIDS Society, which the Deputy Director for Extramural Research is helping to organize.

In July, the Deputy Director delivered a paper at the 15th International Congress of Chemotherapy in Istanbul, Turkey, on recent developments in chemotherapy with respect to treatment for AIDS. He also attended a WHO meeting in Geneva in March to develop a paper on the state of the art of antiviral drugs and to formulate a policy on the use of antiviral drugs and interferon in the prevention and cure of common viral diseases. In May, he served on the faculty of the Advanced Study Institute, North At-

lantic Treaty Organization, and gave a lecture on antiviral drug development.

Office for Protection From Research Risks

DHHS Policy for the Protection of Human Subjects in Research: Within the Office of Extramural Research is the Office for Protection From Research Risks (OPRR), which implements regulations for the protection of human subjects of biomedical and behavioral research supported by DHHS. The DHHS regulations are found in Title 45, Part 46 of the Code of Federal Regulations (45 C.F.R. 46).

Any institution, foreign or domestic, that proposes to engage in research involving human subjects and is supported in whole or in part by DHHS is required to negotiate an Assurance of Compliance for the Protection of Human Research Subjects; that is, a statement of the institute's commitment to comply with the requirements of 45 C.F.R. 46. An assurance is a written document negotiated between an institution that conducts or supports research and OPRR, acting on behalf of the Secretary, DHHS. It sets forth the procedures the institution will use to protect human research subjects and reflects local administrative structures within which the research will be conducted. Assurances with institutions in foreign countries are Single Project Assurances. These are documents specifically developed for each research project involving human subjects and supported in whole or in part by any component of DHHS.

In FY 1987, OPRR negotiated 88 assurances with institutions in 26 countries. OPRR also worked with the NIH Deputy Director for Intramural Research, the Clinical Center, and Fogarty International Center to refine a human subjects review system for collaborations in foreign countries by NIH intramural scientists.

In June, OPRR staff organized a roundtable discussion at the Third International Conference on AIDS, on the subject "Ethical and Legal Implications of AIDS: The International Perspective." Panelists represented Australia, Netherlands, Switzerland (WHO), United Kingdom, and United States.

The Director of OPRR represented the United States at the Summit Bioethics Conference held in Ottawa, Canada, in June. The meeting, titled "Towards an International Ethics for Research Involving Human Subjects," addressed the need for continuing development of national standards of ethics in research with human subjects. The growing interdependence of nations throughout the world has stimulated a need for internationally agreed-upon standards and practices based on a careful continuing dialogue and reflection of values. The meeting in Canada was the fourth in a series of annual bioethics summit meetings initiated by the Prime Minister of Japan in 1984.

OPRR continued to work closely with the Fogarty International Center, the Office of International Health, and the U.S. Embassy in New Delhi, India, to develop an appendix concerning the protection of human subjects to the bilateral agreement for the Indo-United States Vaccine Action Program.

Welfare of Animals in Research: OPRR also is charged with implementing policies concerning the welfare of animals in research supported by DHHS. In September 1986, the revised *Public Health Service Policy on Humane Care and Use of Laboratory Animals* was issued. Public Health Service policy requires institutions to establish and maintain proper measures to ensure the appropriate care and use of all animals involved in research, research training, and biologic testing activities supported by PHS. The policy is applicable to all institutions, domestic or foreign. Institutions in foreign countries that receive PHS support for activities involving animals must comply with the policy or provide evidence to PHS that acceptable standards for the humane care and use of the animals will be met. OPRR can provide additional information on implementation of the policy.

Office of Disease Prevention

The Office of Disease Prevention was established within the Office of the Director in FY 1987. The Office of Medical Applications of Research (OMAR), the Nutrition Coordinating Committee (NCC), and the Division of Disease Prevention are components of this new office. OMAR and the National Institute of Diabetes and Digestive and Kidney Diseases collaborated with the Institut National de la Santé et de la Recherche Médicale, France, on a consensus development conference on diet and exercise in non-insulin-dependent diabetes mellitus. In addition, the OMAR Acting Director chaired an international consensus development conference in Israel in April on magnetic resonance imaging and positron emission tomography. OMAR, WHO, and the Israeli Ministry of Health co-sponsored the meeting.

Office of Research Services

The Office of Research Services is responsible for the management of technical and selected administrative services to all NIH components. It also provides national leadership in research safety policy and

methodology. This office comprises three primary units: the Division of Administrative Services, the Division of Engineering Services, and the Division of Safety.

Bilateral Agreements and Other Country-to-Country Activities

India: During FY 1987, the Associate Director for Research Services organized and taught a 1-week course on nuclear magnetic resonance (NMR) at the Indian Institute of Science in Bangalore. He also consulted on the organization of an *in vivo* NMR center that is being planned for Delhi.

The Associate Director for Research Services also collaborated with officials at the U.S. Embassy in planning a symposium in honor of the NIH Centennial and in arranging for the organization of an NIH alumni group in India.

Collaborative research projects and exchange visits began under an agreement approved last year between the NIH Intramural Research Program and the Center for Cellular and Molecular Biology, Hyderabad, a component of the Indian Council for Scientific and Industrial Research.

Activities With International and Multinational Organizations

The Division of Safety continues to provide biosafety support to WHO through its WHO Collaborating Center for Applied Biosafety Programs and Research. In February 1987, the staff official detailed to WHO, Geneva, as Coordinator of the Special Program on Safety Measures in Microbiology returned to the Division of Safety as Assistant Director for Extramural Activities. In this capacity, he coordinates the activities of other WHO Biosafety Collaborating Centers and advises WHO on laboratory safety requirements, training, and sources of technical assistance.

In June 1987, the Assistant Director for Extramural Programs, Division of Safety, participated in a meeting in Geneva of the WHO Advisory Committee on Health Research's Subcommittee on Transfer of Technology to Developing Countries. At that time, he also served as a technical advisor to WHO's Division of Communicable Diseases, the Special Program on AIDS, and the International Program on Chemical Safety.

Under the auspices of PAHO, a senior safety and health specialist provided onsite technical assistance in laboratory design to the Instituto Nacional de Dermatologia, Caracas, Venezuela, in June 1987. He consulted with the Director, research staff, architect, and engineers on primary and secondary containment concepts for research laboratory modules under consideration by the institute.

The Chief of the Safety Operations Section, Occupational Safety and Health Branch, participated in a workshop on laboratory administration and safety in Mexico City in October 1986. He lectured on the management of biological and chemical safety programs. The Mexican Ministry of Health and PAHO sponsored the workshop.

International Conferences, Seminars, and Meetings

The Associate Director for Research Services attended the biennial General Assembly of the International Union of Pure and Applied Chemistry in Boston, Massachusetts, where he was appointed chairman of the organization's Committee on Publications.

Chapter III
John E. Fogarty International Center for Advanced Study in the Health Sciences

Introduction

The John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) was established in 1968. Its mission, outlined in P.L. 99-158, Section 482, is to provide a focus and organizational mechanism for NIH activities in international biomedical research. The general purposes of the FIC are to:

- Facilitate the assembly of scientists and others in the biomedical, behavioral, and related fields for discussion, study, and research relating to the development of health sciences internationally;
- Further international cooperation and collaboration in life sciences research programs, conferences, and seminars;
- Provide postdoctoral fellowships for research training in the United States and abroad and promote exchanges of senior scientists between the United States and other countries;
- Coordinate the international activities of the National Institutes of Health; and
- Receive foreign visitors to the National Institutes of Health.

The FIC discharges its responsibilities through four programs: Advanced Studies, International Research and Awards, International Coordination and Liaison, and Foreign Scientists Assistance. Throughout FY 1987, the FIC Director was also the NIH Associate Director for International Research, in which capacity he advised the NIH Director on international policies and procedures related to health research.

Highlights for the FIC during FY 1987 included the major responsibility for organizing the Third International Conference on Acquired Immunodeficiency Syndrome (AIDS). The conference was attended by more than 7,000 persons, including over 900 members of the media.

The FIC developed guidelines in FY 1987 to begin awarding in FY 1988 new AIDS research fellowships for individual scientists and institutional grants for collaborative AIDS research.

As part of the NIH Centennial observances, the FIC organized a special symposium co-sponsored by the Institut Pasteur of France. The Fogarty Center also sponsored a Centennial symposium of Scholars-in-Residence, the first such meeting of current and former scholars.

In early 1987, the FIC helped organize and participated in a meeting of representatives of the Ministers of Health of seven countries of the Eastern Mediterranean region to study yaws and other endemic treponematoses.

Another important event was an international symposium entitled "Research Towards Rabies Prevention," held at the Pan American Health Organization (PAHO) in Washington, D.C. During the year, the FIC obtained final information from the United States and six Latin American countries for a cooperative project with the World Health Organization (WHO) and PAHO on "The Role of International Collaboration in Strengthening Health Research in the Americas." Recommendations are being developed to enhance biomedical science collaboration in the Americas.

In response to the Reagan-Gorbachev summit meetings and ongoing efforts to reinvigorate cooperative activities with the Soviet Union, the Eighth U.S.-U.S.S.R. Joint Health Committee Meeting was held in Bethesda, Md., in April 1987. The U.S.-Poland Joint Board on Scientific and Technological Cooperation resumed its collaboration in 1987 after a 5-year hiatus. A joint U.S.-Brazil Presidential Panel met twice in 1987 and recommended collaborative research on infectious diseases, cardiovascular diseases, and the neurosciences. Memoranda of Understanding also were signed with Austrian and Bulgarian organizations. Details on these activities are

discussed under "International Coordination and Liaison."

During FY 1987, 20 scientists participated in the Scholars-in-Residence Program. They studied areas as diverse as ethical uses in human genetics to liver disease in developing countries. One hundred International Research Fellowships were awarded to scientists from 34 countries who carried out research in 25 states. Forty-seven U.S. scientists from 25 states received Senior International Fellowship Awards to pursue collaborative research in 16 nations.

Advanced Studies

The goal of the Advanced Studies Program is to study, review, and evaluate major areas of biomedical research and to facilitate international scientific communication. Advanced studies in the health sciences are carried out under the International Studies and Scholars-in-Residence Programs.

International Studies Program

The purpose of the International Studies Program is to foster and conduct advanced studies in health sciences. The program draws on the expertise available in the Scholars-in-Residence Program and on scientists within institutes of the NIH, as well as outside groups and consultants, to formulate recommendations and plans related to international aspects of biomedical research. Its specific mandates are to:

- Identify international health issues that should receive the attention of the NIH institutes as well as the FIC;
- Address problems concerning international aspects of biomedical and behavioral research, research manpower training, and the transfer of research results to bring new knowledge to bear where it will benefit international health;
- Identify barriers to the international transfer of research findings and develop methods to overcome these barriers;
- Formulate questions to be answered in choosing among alternative programs and develop a plan for action by the FIC, the appropriate categorical institutes, or other Federal agencies; and
- Provide management support for selected FIC and NIH international conferences.

The primary considerations in choosing topics for study are a need to conduct a special study in an area not otherwise being adequately addressed, scientific significance, and/or potential to advance scientific knowledge and health worldwide.

Thus far, the International Studies Program has concentrated its efforts on an examination of disease candidates for improved control and potential eradication. There have been subsequent conferences on measles, polio, yaws and other endemic treponematoses, prevention of congenital rubella infection, research toward rabies prevention, and research toward global control and prevention of tuberculosis. In the past, the program has emphasized infectious diseases; in the future, it will consider both chronic and infectious diseases. A key theme will be efforts to enhance disease prevention from an international perspective. The program will emphasize scientific studies conducted by individuals or small groups of experts as opposed to major international conferences. Conferences and workshops will continue to be used where appropriate.

The program will be structured around four study areas:

- Identification of geographic variations and trends in disease etiology and epidemiology considering genetic, cultural, and environmental determinants;
- Development and demonstration of concepts and strategies to improve cooperation among biomedical researchers worldwide, including strategies to increase involvement of U.S. academic and private institutions in international biomedical and disease prevention research;
- Development and demonstration of novel and improved methods for the dissemination and exchange of biomedical research technologies internationally; and
- Identification of research needs and opportunities that would enhance disease prevention and control internationally, including assessing the potential to control or eradicate diseases. An example of this involves special attention to AIDS and AIDS-related activities.

Major program accomplishments for the past year are discussed below.

Poliomyelitis: The greatest impact of renewed efforts following the 1982 FIC International Symposium on Poliomyelitis Control has been observed during the past year in the Americas. PAHO's program to eliminate polio from the Americas by 1990 using the Sabin oral polio vaccine plus national vaccination strategies has reduced the number of countries in the region reporting polio to 12 nations, down

from 19 countries the previous year. Coverage of children immunized against polio now exceeds 80 percent in all polio-endemic countries of the Americas. Dr. Albert Sabin, Senior Medical Science Advisor at the Fogarty International Center, has assisted PAHO in its planning for regional elimination of poliomyelitis. The FIC and PAHO supported publication of the proceedings of the international symposium—the state-of-the-art study of polio—into Spanish, which has greatly facilitated this overall effort.

Measles: There is a clear need for a more immunogenic measles vaccine that would be effective in the presence of maternal antibodies and allow children in the developing world to be immunized earlier, perhaps even at 6 months of age. Approximately 30 percent of children who die of measles in developing countries do so before 9 months of age, the earliest age at which the current vaccine is given effectively.

Dr. Sabin has been instrumental in the development and testing of a new vaccine, the Edmonston-Zagreb (*Ikic strain*) grown in human diploid cells (HDC). Preliminary work has indicated that this vaccine can effectively immunize infants younger than 9 months of age. A randomized, controlled vaccine trial is currently under way in Mexico, funded by the U.S. Agency for International Development's Vaccine Development and Health Research Program, using a participating Agency Services Agreement involving the Centers for Disease Control, the Food and Drug Administration, and the FIC.

Yaws and Other Endemic Treponematoses: In FY 1987, the FIC helped organize and participated in a meeting of representatives of the Ministers of Health of seven countries of the Eastern Mediterranean region to determine the magnitude of bejel (endemic syphilis) and yaws in that area of the world. This was a component of a global study that has shown that these diseases are currently prevalent in 50 countries. The final portion of the FIC-WHO effort to determine the extent of these diseases and the need for control programs will be completed in April 1988, when PAHO reports on its study of seven countries in the Americas.

The World Health Organization requested that an FIC staff person work in Geneva on a short-term consultantship to assist in the preparation of WHO's Program for the Control of the Endemic Treponematoses. This project was completed in March 1987. Funds are being made available by WHO, and additional resources are being requested of major international organizations to treat the estimated 2.5 million victims of these diseases, 75 percent of them children.

AIDS: The Third International Conference on AIDS, held June 1–5, was a major accomplishment in FY 1987. Total attendance, including over 900 news media representatives, topped 7,000. Information was presented in such areas as virology, immunology, and epidemiology. The Fogarty International Center assumed a major responsibility for organizing this conference on behalf of the NIH and the Public Health Service. The conference included seven plenary sessions, more than 200 individual scientific presentations, 20 roundtable discussions, and 1,000 poster presentations covering many aspects of AIDS research and control.

Rabies: As part of an effort to evaluate the worldwide problem of rabies, the FIC, in collaboration with WHO, PAHO, the Centers for Disease Control, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the U.S. Department of Agriculture, and the Wistar, Pasteur, and Merieux Institutes, convened an international symposium November 3–5, 1986, on "Research Towards Rabies Prevention." The symposium was held at PAHO in Washington, D.C. The meeting focused on the feasibility of controlling human rabies through rabies control in wild and domesticated animals. It reviewed the global rabies problem, research needs, and prevention strategies to achieve global rabies control. Two hundred experts from 25 nations participated in this event. Symposium participants drew four conclusions:

- Human rabies can be prevented if wildlife and domesticated animals are well immunized; research is needed on how better to educate the public and professionals about the natural history of rabies and the importance of dealing with this animal disease.
- Rabies continues to plague developing countries via domesticated animals as well as wildlife, while in the developed nations, human rabies infection is broken by massive rabies vaccination programs of household pets.
- Research on oral vaccines that can be incorporated in bait is promising and has proved successful in controlling fox rabies in Canada, the Federal Republic of Germany, and Switzerland; unfortunately, no comparable vaccine is available for other wild animals or dogs, although preliminary data from trials with recombinant vaccinia viruses are promising.

- Rabies immunoglobulin and human diploid cell vaccine are the current standard treatment and prevention modalities against human rabies in developed countries. Emphasis should be on developing inexpensive, effective prophylactic treatments that have no neurologic side effects, are adaptable to developing countries and in particular to tropical climates, and can be applied without extensive training of personnel.

Antibiotics: The FIC recently supported a study of antibiotic use and antibiotic resistance worldwide that involved participants from more than 30 countries. The study results were published in the May–June 1987 issue of *Reviews of Infectious Diseases.*

Scholars-in-Residence Program

Through the Scholars-in-Residence Program, established in 1969, outstanding scientists and scholars are invited to the NIH campus in Bethesda, Maryland, to interact with the scientific community and to engage in free-ranging study of subjects of their own choosing. They also are expected to participate in regular seminars and other activities, such as conferences and workshops, held at the Fogarty International Center. Some scholars are invited specifically because their research plan is on a topic under study by the FIC.

An important feature of this program is the opportunity it offers the scholars to focus on research and writing that they might not have time to undertake otherwise. Since 1969, a total of 156 men and women have participated in the program. Most have come from Western Europe, North America, Japan, or Australia.

Six new scholars began their scholarships in FY 1987; 14 other scholars returned during the year to continue their studies on advanced topics. One particularly interesting project involved the repair of a serious genetic defect that affects liver function. In collaboration with a group of scientists from the National Heart, Lung, and Blood Institute (NHLBI), a U.S. scholar showed that it may be possible to repair the defect by introducing a gene into the defective liver cells and thus provide the missing enzyme. The same scholar carried out a number of collaborative studies with other groups at the NIH on resistance to anticancer drugs.

A Japanese scholar, who is a world-renowned expert on complex carbohydrate molecular structure, studied the isolation of the sugar chain components of lipoproteins involved in atherosclerosis, which is a major cause of coronary artery disease. In collaboration with scientists at NHLBI, he prepared a sufficient quantity of the material to begin detailed structural studies that should help in understanding how these lipoproteins are metabolized and how they interact with specific sites in the lining of arteries to cause atherosclerotic lesions. Parts of these collaborative studies are being conducted at the Tokyo University Institute of Medical Sciences, which has an active program to study complex carbohydrate structure.

An Israeli scholar devoted most of his time at the NIH to the study of simian AIDS in collaboration with groups at NINCDS interested in neurologic manifestations of human immunodeficiency virus (HIV), the cause of AIDS in humans. An important aspect of research on AIDS is the development of animal models of the disease. Simian AIDS is analogous to the human disease in many respects and is proving useful in drug and vaccine trials.

A Norwegian scholar known for his work in clinical genetics of common diseases conducted a study and organized a workshop, with FIC support, to consider strategies for controlling cancer through the use of genetics. A significant paper was published in the *American Journal of Human Genetics* (41:63–69, 1987) which has led to a series of conferences abroad to discuss ways of implementing recommendations for the use of such knowledge in clinical practice.

An Australian scholar spent a year at the NIH writing a textbook on hepatitis A. He conducted a workshop on non-A, non-B hepatitis at which participants from Burma, India, U.S.S.R., and United States compared information on strains of the putative virus in order to establish criteria for its identification in clinical practice and for public health control measures. As a result of being freed from his administrative responsibilities for a year, this scholar was able to complete numerous reviews and two monographs. He also contributed significantly to the organization of the program for the Third International Conference on AIDS.

During the year, 21 articles by Fogarty scholars were published in recognized journals.

International Research and Awards

The FIC supports and administers several international fellowship programs including the Senior International Fellowship and International Research Fellowship Programs. The fellowships facilitate the exchange of research information by providing opportunities for U.S. researchers to work in foreign laboratories and by enabling foreign scientists to pursue their research interests in U.S. laboratories.

Senior International Fellowships

The Senior International Fellowship (SIF) Program provides opportunities for established U.S. biomedical or behavioral researchers to conduct collaborative research in foreign institutions. SIF awardees enhance the exchange of ideas and information about the latest advances in specific areas of medicine, both basic and clinical. During FY 1987, U.S. institutions nominated 90 scientists for SIFs, 47 of whom were funded. Table III–1 lists the host countries that received SIF awardees in 1987.

Examples of collaborative research projects undertaken by SIF awardees follow:

- Schistosomiasis is a major public health problem, afflicting more than 200 million people in developing nations. Understanding how the immune system responds to and controls the infection is important for the development of an effective vaccine. Using immunofluorescent and electron microscopy, an SIF from Brown University collaborated with scientists in London, England, to examine the sensitivity of larval schistosomes to antibodies. They found that the antibody present in serum from rats resistant to reinfection with *Schistosoma mansoni* bound specifically to the parasites and immobilized them. Knowledge gained from these studies will enhance understanding of host-parasite interactions and serve to focus efforts in vaccine development.
- An SIF from Brigham and Women's Hospital, Boston, working with researchers in the United Kingdom, has developed a technique to enable radiologists to detect tumors in the liver and spleen at an earlier and potentially more treatable stage.

Table III–1

SENIOR INTERNATIONAL FELLOWSHIP AWARDS BY COUNTRY/AREA OF APPLICANTS, FY 1987

Country/Area	No. of Awards	Country/Area	No. of Awards
AMERICAS	1	**EUROPE**	38
Brazil	1	Austria	1
		Belgium	1
		Denmark	1
		Finland	1
ASIA AND FAR EAST	8	France	5
		Germany, Fed. Rep.	1
Australia	3	Netherlands	3
India	1	Sweden	1
Japan	1	Switzerland	3
New Zealand	1	United Kingdom	21
Taiwan	2		
MIDDLE EAST	0		

Most Senior International Fellows publish one or more research papers as a result of their fellowship year abroad. However, the long-term benefits of the fellowship often are realized years later.

One former SIF conducted collaborative research in Japan, applying and validating air pollution source models to samples of Tokyo smog collected by a Japanese Government agency. Despite conceptual and language problems, the Japanese Government and the U.S. investigator worked together to develop and test models to evaluate atmospheric hydrocarbon data. The experience gained from these fellowships enabled the U.S. investigator to obtain funding from the Environmental Protection Agency to develop similar organic source models for air pollution problems in the United States. The collaboration with the Japanese researchers has resulted in six publications, three presentations at scientific meetings, and three environmental analysis monographs.

Another former SIF credits his fellowship year abroad as a key factor in directing his research into diabetic nephropathy. Because so much of diabetic nephropathy research is conducted in European laboratories, this researcher has continued the scientific collaborations that were established during his SIF term with researchers at laboratories in Denmark and the United Kingdom. As a result, he will be sponsoring the Third International Diabetic Nephropathy Meeting in Minneapolis in 1989; the first two meetings were held in Denmark.

Foreign Fellowships for U.S. Scientists

On behalf of foreign organizations, the FIC administers nine postdoctoral research fellowship programs for U.S. scientists to study abroad. The FIC announces the availability of fellowship support and arranges for the initial review for scientific merit by the Division of Research Grants for the following foreign organizations:

- Academy of Finland;
- French National Institute of Health and Medical Research;
- Irish Health Research Board;
- Israeli Ministry of Health;
- Norwegian Research Council for Science and the Humanities;
- Swedish Medical Research Council; and
- Swiss National Science Foundation.

The FIC also announces the availability of fellowships supported by the Alexander von Humboldt

Foundation in the Federal Republic of Germany and by the National Science Council in Taipei, Taiwan.

All funding decisions are made by the foreign organization that sponsors the program.

Fellowship Programs for Foreign Scientists

International Research Fellowships: The International Research Fellowship (IRF) Program enables postdoctoral biomedical or behavioral scientists in the formative stages of their research career to extend their research experience in a U.S. laboratory. These fellowships support collaboration between distinguished U.S. scientists and qualified scientists in other countries to study health-related problems of mutual interest.

During FY 1987, 55 nominating committees were officially active; 157 applications from 39 nominating committees were reviewed. Subsequent to scientific peer review conducted by the NIH, 100 were funded to do research in 25 different states of the United States. Table III–2 shows recipient countries of fellowship awards.

Table III–2

INTERNATIONAL RESEARCH FELLOWSHIP AWARDS BY COUNTRY/AREA OF APPLICANTS, FY 1987

Country/Area	No. of Awards	Country/Area	No. of Awards
AMERICAS	20	**EUROPE**	47
Argentina	4	Belgium	4
Bolivia	1	Denmark	2
Brazil	4	Finland	6
Canada	3	France	6
Colombia	1	Greece	1
Mexico	4	Ireland	3
PAFAMS[a]	1	Italy	3
Uruguay	1	Norway	2
Venezuela	1	Poland	5
		Spain	4
		Sweden	5
		Switzerland	1
AFRICA	5	United Kingdom	3
		Yugoslavia	2
Ethiopia	1		
Nigeria	4		
ASIA AND FAR EAST	24	**MIDDLE EAST**	4
Australia	2	Israel	3
China	3	Lebanon	1
India	2		
Japan	5		
Korea	3		
New Zealand	3		
Thailand	2		
Taiwan	4		

[a]Pan American Federation of Association of Medical Schools.

Examples of collaborative research projects undertaken by IRF awardees follow.

Systemic lupus erythematosus (SLE) is a common chronic systemic inflammatory disease that predominately affects women of childbearing age. The cause of the disease is unknown, and no specific treatment is available. Because anti-deoxyribonucleic acid (DNA) antibodies are a hallmark of SLE, an International Research Fellow from France and his U.S. sponsor from Tufts University School of Medicine have focused on the analysis of their binding specificity, their idiotypic expression, and the diversity of their variable genes. Along with other studies, such approaches may reveal some clues on the mechanisms of anti-DNA hyperproduction, which may elucidate the origin of autoimmunity.

An IRF from Chile also worked on SLE and studied the immunotoxin therapy of lupus nephritis in autoimmune mice. By treating mice with cytotoxic drugs conjugated to mouse monoclonal anti-idiotypic antibodies, he significantly reduced the production of anti-DNA antibodies and improved both renal function and survival of these mice. The information derived from murine models of this disease may encourage the development of anti-idiotypic therapy for human SLE. These studies were done in collaboration with scientists from the University of California, Los Angeles Medical School.

The IRF Program is recognized as a major link between the United States and the Finnish health research community. Visits to the United States by the 129 former IRFs continue to influence the development and activity of the Finnish public health system. Contacts initiated by the IRF Program have grown into an effective international network for the exchange of scientific information through symposia, cooperative projects, and research communications. Almost one-half of former IRFs are now professors or associate professors in Finnish universities or research institutes. Of these, six investigators have continued to be funded through NIH research grants and contracts in the areas of bone marrow transplantation, effects of lead in the workplace on reproduction, lymphoid cell differentiation, receptor binding, and structural studies of red blood cell glycoproteins.

International Neurosciences Fellowships: The International Neurosciences Fellowship Program, established in 1977 in cooperation with NINCDS and WHO, is administered by the FIC with funds provided by NINCDS. In FY 1987, two awards were made to scientists from developing countries to conduct collaborative research in epilepsy and stroke.

International Tropical Diseases Research Fellowships: The FIC, in cooperation with NIAID and the United Nations Development Program/World Bank/WHO Special Program for Research and Training in Tropical Diseases, has established a limited number of postdoctoral fellowships in tropical diseases. Candidates for these fellowships are from countries in which the following diseases are endemic: malaria, schistosomiasis, leishmaniasis, trypanosomiasis, filariasis, and leprosy. No awards were made in FY 1987.

Collaborative Programs for U.S. and Foreign Scientists

Individual Biomedical Health Scientist Exchange Programs: Under individual cooperative agreements, the FIC administers biomedical and health scientist exchange programs with eight countries: Austria; Bulgaria; France (CNRS); Hungary; Poland; Romania; U.S.S.R.; and Yugoslavia. Table III–3 provides summary data on these exchange programs.

Special Foreign Currency Program: The Special Foreign Currency Program supports biomedical research and the translation and dissemination of health science information in selected countries. The program was initially financed with U.S.-owned foreign currency determined to be in excess of the immediate needs of the United States and popularly referred to as "P.L. 480 Funds." Over the extended life of this program, these funds have been depleted, one country at a time.

To maintain the scientific collaborations developed with these funds, the Department of State, when funds are depleted in a country, negotiates "joint funds" customarily with matching deposits of foreign currency and Joint Boards to administer the funds under terms accommodating to country circumstances (which may vary by country and year). Portions of these funds are allocated to the NIH. The countries where funds are currently available are India, Poland, and Yugoslavia. (Burma is designated an excess currency country, but the Public Health Service has had no program there in recent years.)

A unique feature of the program is its collaborative character. Research proposals must represent a joint effort and mutual interest of the U.S. and foreign scientists within their areas of professional interest and competence. The program comprises projects covering a wide spectrum of biomedical research. Emphasis is on using resources unique to the host country.

The currencies are not convertible to U.S. currency; therefore, no dollars are available for items such as equipment. Funds may not be used without written consent of the foreign government. Central coordinating committees and channels exist in all countries to provide a review for scientific merit and concurrence with national policies, procedures, and priorities concerned with health and science, as well as political, economic, and other factors. A research proposal may originate with a scientist in either the United States or a foreign country. The collaborator in the foreign country where the research is done must submit an application to the NIH through channels designated by the foreign government via the U.S. Embassy. The award will be made to the foreign institution. No funds for research costs are awarded to the institution of the U.S. collaborator;

Table III–3

EXCHANGES OF U.S. AND FOREIGN SCIENTISTS SINCE INITIATION OF PROGRAMS AND FY 1987

Country	Year Initiated	Maximum Person-mos. (per year)	Average Length of Stay (person-mos.)	FY 1987				Total U.S. Scientists to Country (person-mos.)	Total Country Scientists to U.S. (person-mos.)
				U.S. Scientists to Country	No. of Person-mos.	Other Scientists to U.S.	No. of Person-mos.		
Austria	1987	30		0	0	0	0	0	0
Bulgaria	1987	15		0	0	0	0	0	0
France (CNRS)	1979	75	9.5	6	24.0	11	73.0	342.0	554.5
Hungary	1982	12	1.5	0	0	3	7.4	4.6	7.4
Poland	1979	30	3.5	2	1.1	3	2.8	26.5	69.8
Romania	1967	24	1.4	0	0	0	0	33.5	100.5
U.S.S.R	1961	5	2.0	2	1.7	8	6.4	319.0	553.3
Yugoslavia	1979	unspecified	2.3	0	0	0	0	7.5	12.7

however, travel funds are provided for visits of the U.S. collaborator to the foreign institution.

India: The Indo-U.S. Science and Technology Subcommission and its Working Group on Health, Medical, and Life Sciences has provided the basis for extensive collaborative activity with Indian scientists since 1974. Selection and review of individual projects has been the responsibility of Indian research institutions and cognizant government departments and ministries.

In anticipation of depletion of the balance of U.S.-owned Indian rupees and removal of the designation of "excess" for these funds at the end of FY 1985, legislation was enacted to establish the U.S.-Indo Fund for Cultural, Educational, and Scientific Cooperation (USIF) with a capitalization of $110 million equivalent in rupees. The Indian Government signed the agreement January 9, 1987, for use of these funds under the conditions that there be no matching by India and that the principal and interest be expended to deplete the fund within 10 years. During the 2-year period between removal of the excess status, when what had imprecisely but popularly become known as "P.L. 480" funds were no longer available and at the end of FY 1987, the program was continued with interim USIF funds that could be committed at NIH discretion. In subsequent years, the use of USIF funds is expected to be subject to procedures, policies, and programs developed jointly by the United States and India for allocation and disposition.

In addition to the longstanding collaboration under the Subcommission, two major research programs with separate identities are supported with rupees of the NIH Special Foreign Currency Program. These are the Science and Technology Initiative and the Vaccine Action Program. The Science and Technology Initiative includes a well-defined research program focusing on prevention of blindness, fertility and infertility control, and immunology as it pertains to malaria, filariasis, leprosy, and tuberculosis.

The Vaccine Action Program was proposed by the Subcommission's Working Group on Health, Medical, and Life Sciences at a meeting in April 1985. The concept was subsequently developed into a program and set forth in a formal agreement that was signed by the Government of India on July 18, 1987. On the U.S. side, this program is a joint effort of the Public Health Service (PHS) and the Agency for International Development. It will involve intramural scientists of the NIH and other PHS agencies and researchers in U.S. universities in cooperative vaccine research and development, production, and quality control activities. The areas of interest are other than those included in the Science and Technology Initiative, such as rotavirus and other diarrheal diseases; typhoid; cholera; non-A, non-B hepatitis; hepatitis B; rabies; pneumonia; and pertussis.

Poland: A meeting of the U.S.-Polish Joint Committee for Cooperation in the Field of Health was held in Washington, D.C., on January 26, 1987. The Polish delegation presented 11 proposals for consideration at this meeting. Two projects were funded concerning studies of the molecular genetics of the muscular dystrophies and the immunology of T suppressor cells. It is anticipated that the new agreement for cooperation in science and technology, accepted in principle but awaiting final signatures by both sides, will provide an impetus for expansion of collaboration.

Yugoslavia: The U.S.-Yugoslavia Joint Board governs and manages the Joint Fund to which each country contributes matching amounts annually under an agreement on scientific and technological cooperation. Approximately $4 million equivalent in Yugoslav dinars is available annually, of which 11 percent is apportioned for PHS projects. Meetings of the Joint Board are held biennially, alternating in Yugoslavia and the United States, at which time annual payments for previously committed projects are authorized and new projects are reviewed and selected for funding. The present PHS program is composed of about 40 projects. The FIC administers this program for the NIH and other PHS agencies.

International Coordination and Liaison

The United States makes significant contributions to the resolution of a broad spectrum of international health problems through its domestic research and related efforts, its cooperative health relationships with other countries, and its participation in the programs and activities of international organizations, notably WHO and PAHO.

The International Coordination and Liaison Program (ICL) facilitates NIH relationships with other countries through arrangements for interaction between scientists, exchange of scientific information, and communications between the NIH and other international organizations or agencies. Program management staff provide policy guidance, coordination, and general oversight for NIH participation in bilateral and other cooperative agreements between the U.S. Government and other countries and link the NIH with other components of the Department of Health and Human Services, the White House Office

of Science and Technology Policy, and the Department of State.

Bilateral Agreements and Other Country-to-Country Activities

Formal intergovernmental agreements may take a variety of forms, ranging from broad scientific and technological exchanges to more specific ones in health. In some instances, a health agreement may be subsidiary to a broader agreement in science and technology. There also are less formal technical-level agreements between the NIH or specific institutes and counterpart foreign institutions for special purposes.

As a basis for cooperation, formal agreements are often required to enhance chances of obtaining increased funding for international collaboration, to make formal arrangements for cost-sharing, and to provide the means for overcoming constraints presented by different social and political systems.

The International Coordination and Liaison Program coordinates NIH participation in 64 bilateral agreements. As designated by the Assistant Secretary for Health, DHHS, the NIH also is the lead PHS agency for bilateral programs with Belgium, France, the Federal Republic of Germany, Hungary, Japan, Poland, Romania, and Yugoslavia.

Significant events that occurred during FY 1987 are described below.

- The Committee on International Science, Engineering, and Technology (CISET) Task Force held meetings to review science and technology relationships with Japan. ICL played a key role in the review and development of a U.S. position on future U.S.-Japan cooperation.
- The Eighth U.S.-U.S.S.R Joint Health Committee Meeting was held in Bethesda, Maryland, April 13–17, 1987. This was the first meeting of the Joint Health Committee since 1979. The Committee reviewed progress in the following areas of NIH involvement: cancer, cardiopulmonary diseases, arthritis, environmental health, eye disease, biomedical communication, and the Health Scientist Exchange Program. The committee also considered the addition of cooperation in primatology. To this end, the ICL played a major role in the planning of the meeting, as well as the preparation of executive summary reports of ongoing activities and proposals for new areas of cooperation.
- In September 1986, President Reagan and President José Sarney of Brazil agreed to undertake a special initiative for implementation of the U.S.-Brazil Agreement in Cooperation in Science and Technology. A U.S.-Brazil Presidential Panel, appointed to review and recommend topics for bilateral cooperation to be considered by a U.S.-Brazil Joint Commission, met in April and July of 1987. In the health area, the panel recommended collaborative research on infectious diseases, cardiovascular diseases, and the neurosciences. ICL coordinated the preparation of NIH submissions to the panel.
- A Memorandum of Understanding between the NIH and the Austrian Science Foundation implementing a Biomedical Research Exchange Program was signed on April 14, 1987. The program supports short- and long-term visits for collaborative research purposes, not to exceed 30 person-months of program time per year for each side.
- On November 4, 1986, a Memorandum of Understanding was signed between the Bulgarian Medical Academy and the NIH. It implements a Biomedical Research Exchange Program supporting short- and long-term visits for collaborative research purposes, not to exceed a maximum of 15 person-months of program time per year for each side.

Multilateral Organizations

The Fogarty International Center represents the NIH in contacts with multilateral bodies such as WHO, PAHO, Standing Committee of the European Medical Research Councils (EMRC), European Science Foundation (ESF), Organization for Economic Cooperation and Development (OECD), and Commission of European Communities. The ICL staff maintain liaison with these organizations and provide NIH positions on agenda issues for the WHO Executive Board meetings, the World Health Assembly, Executive Committee, Directing Council meetings of PAHO and of the Western Pacific Regional Organization Committee, and meetings of ESF and the Standing Committee of the EMRC. The staff also process requests for services of NIH members for WHO and PAHO expert committees.

The FIC, as a WHO Collaborating Center for Research and Training in Biomedicine, continues to provide opportunities for mutually beneficial interaction between the NIH, WHO, and PAHO. In FY 1987, the FIC WHO Collaborating Center adapted to the Southeast Asia region a PAHO/WHO cooperative project on medical entomology in the Americas. The project will stimulate expanded basic research on the entomologic aspects of vector-borne diseases that pose a threat to Americans at home and abroad. Studies in the participating countries will identify

education and training needs for medical entomologists in research and control of major vector-borne diseases and strategies for greater involvement of these specialists in vector control programs. Also, in FY 1987, the FIC obtained final information from the United States and six Latin American countries for the cooperative project with WHO and PAHO entitled "The Role of International Collaboration in Strengthening Health Research in the Americas." The project has investigated how national policies, institutional capability, and the activity of individual scientists influence collaboration in the health sciences. It is expected to develop recommendations for strengthening opportunities for international collaboration among biomedical scientists in the Americas.

Other Liaison Functions

The ICL staff coordinate the visits of principals of ministries of health, national research councils, and multilateral organizations, and in FY 1987 produced more than 35 background briefing books and papers for NIH officials.

ICL staff assist the NIH components by processing foreign grants and contracts for clearance through the Department of State. During FY 1987, the ICL staff processed 188 notifications of proposals to make awards for foreign grants, foreign contracts, or domestic grants with substantial foreign components. In addition, 1,686 notifications for foreign travel of NIH staff were reviewed and forwarded to the Office of International Affairs, DHHS, for approval. The staff also serves as the channel for cable communications through the Department of State to U.S. Embassies abroad.

The FIC Director meets bimonthly with the international program representatives of the NIH components to exchange information and views on NIH international activities. These meetings are organized by ICL staff and frequently include speakers on special issues in international health.

Foreign Scientists Assistance

The Foreign Scientists Assistance Program provides visa and immigration management, personnel, and administrative services to foreign scientists in the NIH Visiting and Guest Researcher Programs as well as for foreign Special Experts, Exchange Scientists, and Special Volunteers engaged in intramural research programs of the NIH. The program provides similar support to the intramural research programs of the National Institute of Mental Health and National Institute on Alcohol Abuse and Alcoholism of the Alcohol, Drug Abuse, and Mental Health Administration and to the Center for Drugs and Biologics of the Food and Drug Administration.

Table III–4

NIH VISITING PROGRAM PARTICIPANTS, FY 1987[a]
RANK ORDER BY COUNTRY/AREA, ALL INSTITUTES

Country	No. of Persons
Japan	362
Italy	135
China	120
India	114
United Kingdom	102
Israel	83
France	57
Germany, Fed. Rep.	48
Canada	46
Poland	35
Spain	35
Australia	33
Korea	30
Argentina	29
Hungary	25
Switzerland	20
Netherlands	19
Brazil	17
Belgium	14
Chile	13
Finland	13
Greece	13

Country/Area With 5–10 Persons	Country With Fewer Than 5 Persons	
Austria	Algeria	Nigeria
Denmark	Bangladesh	Norway
Ireland	Barbados	Pakistan
Mexico	Bahamas	Peru
New Zealand	Colombia	Philippines
Sweden	Costa Rica	Romania
Portugal	Czechoslovakia	Saudi Arabia
South Africa	Egypt	Sierra Leone
Yugoslavia	Ethiopia	Singapore
Taiwan	Ghana	South Vietnam
	Hong Kong	Sudan
	Iceland	Thailand
	Iran	Tunisia
	Jamaica	Turkey
	Jordan	Uganda
	Lebanon	Uruguay
	Luxembourg	Venezuela
	Malaysia	Zaire
	Malta	Zimbabwe
	Morocco	

[a]A total of 1,507 foreign participants from 73 countries and 115 U.S. citizens and permanent residents.

Table III–5

FOREIGN GUEST RESEARCHERS, FY 1987[a]
RANK ORDER BY COUNTRY/AREA, ALL INSTITUTES

Country	No. of Persons
Japan	75
Italy	72
Germany, Fed. Rep.	64
China	48
India	36
Canada	35
France	32
Israel	29
United States (permanent residents)	21
Spain	21
United Kingdom	16
Korea	13
Switzerland	12
Austria	11

Country With 5–10 Persons	Country/Area With Fewer Than 5 Persons	
Argentina	Algeria	Norway
Australia	Bulgaria	Pakistan
Belgium	Burma	Philippines
Brazil	Colombia	Portugal
Chile	Egypt	South Africa
Denmark	Ethiopia	Syria
Finland	Ghana	Türkey
Greece	Hong Kong	Uganda
Mexico	Hungary	Uruguay
Netherlands	Indonesia	U.S.S.R.
New Zealand	Ireland	Yugoslavia
Poland	Kenya	Taiwan
Sweden	Malaysia	
	Mali	
	Mauritania	

[a]A total of 615 Guest Researchers from 54 countries.

NIH Visiting Program

Providing support to the NIH Visiting Program is the major activity of the Foreign Scientists Assistance Program. Scientists who participate in the Visiting Program do so in one of three categories: Visiting Fellows (1–3 years postdoctoral), Visiting Associates (3–6 years postdoctoral), and Visiting Scientists (6 or more years postdoctoral). During FY 1987, 1,622 individuals participated in this program in both the NIH and at non-NIH research institutes. Of this number there were 1,074 Visiting Fellows; 371 Visiting Associates; and 177 Visiting Scientists. In the NIH Institutes only, there were 969 Visiting Fellows, 335 Visiting Associates, and 161 Visiting Scientists (see Table III-4). Awards and appointments in the NIH Visiting Program are by invitation only.

The largest number of participants in the NIH Visiting Program were from Asia, with most scientists (362 in all institutes) coming from Japan, followed by Europe, the Americas, and a few from the Middle East and Africa (see Table III–5). In FY 1987, the NIH initiated a new Intramural Research Training Award to increase opportunities for citizens and permanent residents of the United States.

Guest Researchers and Special Volunteers

Guest Researchers and Special Volunteers are financially supported by their home institution and/or foreign and domestic foundations. Guest Researchers are independent scientists conducting their own research using NIH facilities. During FY 1987, there were 615 foreign Guest Researchers (including 77 in the non-NIH institutes) from 54 countries. The majority of the Guest Researchers were from Europe (298 for all institutes), followed by Asia, the Americas, and a few from the Middle East and Africa. Japan, with 75 participants, and Italy, with 72, had the most representation.

Special Volunteers participate in a directed program of ongoing research. In FY 1987, there were 49 Special Volunteers from 17 countries. This is a new category and presently these scientists work only at institutes of the NIH.

Significant accomplishments of foreign scientists participating in the NIH Visiting Program and Guest Researcher Program appear in reports from the individual research institutes throughout this document.

Volunteer Services

The Volunteer Services Office opened in 1987 to help foreign scientists who come to the NIH settle into the community quickly and comfortably. Volunteers trained by the FIC staff conduct an orientation for scientists of the NIH Visiting and Guest Researcher Programs. They provide information on local housing, furniture, transportation, family and school programs, and social and cultural activities. Foreign scientists are encouraged to contact the Volunteer Services staff at any time during their stay at NIH for help and assistance as needed.

Chapter IV
National Cancer Institute

Introduction

In concert with other Institutes and the Fogarty International Center, the National Cancer Institute (NCI) maintains an active program in the international arena through bilateral agreements, grants and contracts, and active information dissemination by the International Cancer Information Center (ICIC) and the Office of Cancer Communications (OCC). Work of highly qualified scientists is supported also by fellowships, active cooperative projects, and exchanges of personnel and reagents. NCI maintains liaison with international organizations and agencies involved in cancer research and prevention: for example, the Committee on International Collaborative Activities, Organization of European Cancer Institutes (OECI), International Union Against Cancer (UICC), International Agency for Research on Cancer (IARC), and European Organization for the Research and Treatment of Cancer (EORTC). An active role falls upon ICIC and OCC for promotion and facilitation of information exchange on professional and lay levels, respectively. These activities are managed or coordinated by the Office of International Affairs (OIA), which consists of two major segments: (1) the bilateral programs, which are managed directly under the Associate Director, OIA, and (2) information exchange on a worldwide basis, which is coordinated and managed by ICIC.

Cooperative cancer research programs under formal government-to-government bilateral agreements constitute a major segment of the international activities. During FY 1987, NCI participated in nine bilateral agreements with the following countries: China, Egypt, France, Federal Republic of Germany (FRG), Hungary, Italy, Japan, Poland, and U.S.S.R.

Formerly, NCI's orientation was to provide a mechanism for exchanges, contacts, and dissemination of reagents, equipment, and information. Now, there is an emphasis on contribution to long-term collaborative ventures. Single, one-on-one agreements eventually will be replaced by larger core projects, international in flavor, where many countries will be able to participate actively and benefit.

Highlights of Recent Scientific Advances Resulting From International Activities

The NCI European collaborative program continues to be highly successful in providing a regular flow of new compounds into the anticancer screen and an increasing number of new drugs for Phase I and II clinical evaluations.

Through an interagency agreement with the Department of State, NCI operates a Liaison Office in Brussels, Belgium. This office is primarily responsible for coordinating the NCI drug discovery and development program in Europe, in close collaboration with the EORTC and the Cancer Research Campaign (CRC, U.K.).

Contacts have been established with more than 600 suppliers of compounds, including university chemistry departments, chemical pharmaceutical firms, and private laboratories. In 1986, the NCI Liaison Office acquired approximately 2,000 new compounds, which were screened at the Institut Jules Bordet under NCI contract. This represents a significant part of the total number of compounds put into the NCI screen. Compound acquisition has been integrated with the Division of Cancer Treatment's Drug Development Program.

The Chinese Academy of Medical Sciences (CAMS) is conducting two double-blind, placebo-controlled nutrition intervention trials using multiple vitamin-mineral supplements to evaluate the relationship between such supplements and the prevention of esophageal cancer. One trial is being conducted in

patients diagnosed with esophageal dysplasia (n = 3,400) and the other in the general population (n = 30,000).

In a cooperative project with the Government of Finland, three studies are being conducted to:

- Determine if either beta-carotene or alpha-tocopherol supplementation is effective in preventing lung cancer in smokers;
- Assess the role of fats, selenium, and vitamins A, E, and C in breast cancer development; and
- Evaluate the relationship of intake of various nutrients to subsequent cancer.

Cancer epidemiology has been given the highest priority under the U.S.-China program, but cooperation also extends to areas of molecular biology and other disciplines in cancer etiology. Collaborative epidemiologic studies to identify the environmental determinants of esophagus, lung, and stomach cancers and choriocarcinoma neared completion this year in four areas of China at high risk for these malignancies. In addition, a collaborative investigation continues in Shenyang to evaluate air pollution from industrial sources and home heating as a risk factor for lung cancer. A vitamin intervention trial also continued in an area of north-central China where rates of esophageal cancer are the highest in the world and where there are chronic deficiencies of several micronutrients.

A project in the tumor biology area concentrated on the development of a mast cell model system to analyze the underlying mechanisms that determine whether progenitor mast cells self-replicate or generate differentiated erythroid cells.

Under the EORTC Research Training Program, initiated about 2 years ago, 15 fellowships are awarded annually on a cost-sharing basis between NCI and the home institution. During the visit, close ties develop between the host and the guest, leading to long-term collaborations. In addition, cross-training is advocated: the clinicians are exposed to basic laboratories, and a pure bench scientist can experience clinical research. As an extension of this successful program, OIA approached several Japanese organizations to explore the potential for an analogous program in that country.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

Cooperative cancer research programs under formal government-to-government treaties and other forms of bilateral agreement constitute a major segment of NCI's international activities. NCI participates in bilateral agreements with the following institutions and countries:

- The Cancer Institute (Hospital), Chinese Academy of Medical Sciences, under the U.S.-China Accord for Cooperation in Science and Technology (1979);
- The Cairo Cancer Institute (1975), under the aegis of the agreement between the United States and the Arab Republic of Egypt;
- The Ministry of Science and Technology of the Federal Republic of Germany (1976);
- The French Institut National de la Santé et de la Recherche Médicale (INSERM) (1975), under the earlier NIH agreement with INSERM;
- The National Institute of Oncology, Budapest, Hungary (1981);
- The National Cancer Institute of Milan and the Institute of Oncology of Genoa, Italy (1977);
- The Japan Society for the Promotion of Science (1974);
- The Institute of Oncology, Warsaw, Poland (1976), under the U.S.-Poland agreement; and
- The All-Union Cancer Research Center, Moscow, U.S.S.R. (1972).

These bilateral scientific programs between NCI and its counterpart foreign institutions contribute significantly to the overall international health policy of the United States. Cancer is a global health problem that forces this country to look beyond its national borders and concerns. A summary of activities under each of NCI's bilateral programs follows.

China: Collaborative U.S.-China epidemiologic studies were conducted largely through NCI contracts from the Division of Cancer Etiology. OIA provided administrative assistance on exchange scientists. The projects are:

- Lung cancer study in Shanghai;
- Esophageal cancer study in Linxian;
- Stomach cancer study in Shandong Province;
- Choriocarcinoma study in Beijing;
- Lung cancer study in Shenyang;
- Cervix and penis cancers study in Hunan;
- Thyroid nodules and cancer study in Guangdong Province;
- Benzene workers study;

- Silica-exposed workers study;
- Yunnan tin workers cohort study; and
- Linxian intervention trial.

Egypt: The Agency for International Development has entered into the Participating Science Agreement with the Office of International Health. The Public Health Service provides supporting funds for the U.S.-Egypt Joint Working Group on Health Cooperation. Clinical and epidemiology studies on non-Hodgkin's lymphoma and leukemia in Egypt are among the projects supported under the new agreement.

France: The NCI-INSERM Committee on Cancer Research is responsible for supporting high-quality research geared to understanding the process of carcinogenesis and various therapeutic studies. Proposals submitted by candidates from each country are reviewed for scientific merit by both American and French committees. This program is very active, and there are many candidates who want to come to the United States and a number of U.S. scientists who want to work in France. During FY 1987, seven Americans visited France, and six French scientists spent varying amounts of time in U.S. laboratories.

Federal Republic of Germany: After several years of minimal activity, the FRG program has grown into one of the more productive relationships between NCI and any European institution. A workshop on mechanisms of initiation was held early in the fiscal year. This workshop, in which 14 Americans participated, was very productive for the exchange of ideas of leading scientists from many institutions. Because the workshop was held in Germany, several European representatives from other countries were able to participate.

Steering committees were formed for both sides. An active program rapidly developed, and the Government of the FRG agreed to fund approved collaborative projects. One planning session was held in Heidelberg in conjunction with the previously mentioned workshop; another followed in the spring of 1987 in Bethesda to plan for the 1988 activities.

Hungary: This program continues to progress satisfactorily. During FY 1987, there were two 6-month exchange visits by Hungarian scientists. One scientist went to Baylor College of Medicine in Houston and worked on a project dealing with nonhistone proteins in normal and tumor cells. The other scientist worked at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, on biochemical alterations induced by gastrointestinal tract toxicants or cytostatic agents in colon cancer. One American scientist traveled to Hungary to work on the relationship between hepatitis B virus and liver cancer.

India: Indian scientists are exploring various methods for collaborative programs in basic research and clinical treatment of cancer. The Department of State has made an initial allocation of funding under the U.S.-India Fund for Cultural, Educational, and Scientific Cooperation. Presently, scientific activities in the field of cancer are limited to the development of new therapeutic agents from indigenous plants and the study of oral cancer and viral oncology, with special reference to nasopharyngeal and cervical cancers.

Several major Indian institutes were visited last year by U.S. scientists, including the Acting Associate Director for International Affairs, NCI, in an effort to explore mutual interests and possible cooperative projects. The Deputy Secretary of the Indian Council for Medical Research came to NCI and spent 2 days of intensive discussions with NCI staff.

Italy: Agreement with Italy, which in the past was concerned only with epidemiology and therapy, has now been expanded to include basic sciences. On both sides, the steering committees were active. In addition to the 21 scientists from Italy who spent a total of 52 person-months in U.S. laboratories, several American counterparts went to Italy to participate in collaborative projects. No symposia or workshops were organized this year as a result of the restrictions in the foreign travel budget, but an active program is planned for next year.

Japan: The most active and largest bilateral program is with Japan. This cooperation occurs through agreement between NCI and the Japan Society for the Promotion of Science. Both sides have a steering committee, and they meet jointly once a year, alternately in Japan and the United States, to review the program's progress and to plan the new program. Currently the program has four areas: etiology, biology and diagnosis, cancer treatment, and interdisciplinary.

During FY 1987, 10 seminars or workshops were held under the aegis of this bilateral agreement, and 13 Japanese scientists visited U.S. institutions.

Korea: A team of U.S. scientists and administrators visited the Korean Advanced Institute of Science and Technology and participated in a joint symposium October 27–28, 1986. They conducted indepth dis-

prevention and control activities are conducted both in the United States and abroad and include liaison development with international scientists, participation in international meetings, and support of contracts and grants in a dozen foreign countries. Descriptions of international studies supported by DCPC follow.

Organ Systems: Investigators at McGill University (Canada) are examining the mechanisms whereby metastatic prostate adenocarcinoma alters skeletal function.

At the Ontario Cancer Institute, one investigator is examining the mechanisms of tumor progression to: (1) study how expression of the epidermal growth factor receptor gene and of the Ha-ras oncogene relate to malignant properties of human tumor cells, and (2) determine whether a horizontal transfer of genes (either oncogenes or those encoding drug resistance) occurs as a result of spontaneous transfection.

Investigators at the Karolinska Institute (Sweden) are attempting to purify, characterize, and determine the toxicologic significance of macromolecules in the tissue that bind xenobiotics and thereby may cause selective accumulation or transport of these compounds in the cat and human prostate gland.

Chemoprevention: In a Phase III clinical trial, researchers at the Istituto Nazionale Tumori (Italy) are evaluating the effectiveness of N-(4-hydroxyphenyl) retinamide in preventing new primary lesions of the contralateral breast in women who have had breast cancer.

In Tanzania, a population of albinos is being studied to document the factors that affect the occurrence of skin cancer, and investigators are conducting a Phase III randomized clinical trial to determine the efficacy of beta-carotene in arresting, inhibiting, or reversing the abnormal clinical and pathological progress of skin changes in the development of skin cancer.

The Chinese Academy of Medical Sciences is conducting a pilot study to investigate the feasibility of an intervention trial of micronutrients for the prevention of lung cancer among tin miners in Yunnan.

Smoking: The University of Waterloo (Belgium) is 1 of 11 intervention centers for the Community Intervention Trial for Smoking Cessation. The trial will determine whether a community-based approach with interventions organized within existing community structures and groups can reach and involve a large proportion of smokers, especially heavy smokers, in successful cessation efforts.

In a study conducted by the World Health Organization, the health effects and attendant economic impacts of tobacco consumption will be examined in three developing countries—Brazil, Egypt, and Thailand.

International Conferences, Seminars, and Meetings

In FY 1987, numerous conferences were arranged under the bilateral agreements in which NCI participates. Table IV–1 contains a summary of these conferences.

Intramural Programs and Activities

International Cancer Information Center: The International Cancer Information Center was established in 1984 to organize and manage the collection,

Table IV–1

NCI INTERNATIONAL CONFERENCES, SEMINARS, AND MEETINGS, FY 1987

Program	Dates	Location	Title
U.S.-Japan	Mar. 26–29, 1987	Honolulu, HI	Marine Natural Products and Cancer Chemoprevention
U.S.-Japan	Mar. 11–13, 1987	Kyoto, Japan	Transacting Factors in Carcinogenesis
U.S.-Japan	Mar. 12–13, 1987	Honolulu, HI	Risk Assessment of Chemical Carcinogenesis
U.S.-Japan	Nov. 10–12, 1986	Seattle, WA	Cellular and Molecular Mechanisms of Oncogenesis and Cancer Immunity
U.S.-Japan	Feb. 12–14, 1987	Honolulu, HI	Regulatory Element in Normal and Transformed Cells
U.S.-Japan	Nov. 7–8, 1986	Tokyo, Japan	Bone Marrow Transplantation
U.S.-Japan	Feb. 3–4, 1987	Honolulu, HI	Innovative Approach to Adjuvant and Neo-Adjuvant Therapy
U.S.-Japan	Mar. 26–27, 1987	Washington, D.C.	Biochemical Pharmacology of Treatment Failure
U.S.-Japan	Jan. 29–30, 1987	Honolulu, HI	Hepatitis B Virus and Primary Hepatocellular Carcinoma
U.S.-Japan	Mar. 23–25, 1987	Los Angeles, CA	Genetics of Human Cancer
U.S.-FRG	Oct. 24–25, 1986	Heidelberg, FRG	The Role of DNA Amplification in Tumor Initiation and Promotion
U.S.-Italy	Nov. 6–10, 1986	Nervi, Italy	Transplacental Carcinogenic Risks to Humans

processing, and dissemination of basic and clinical research information on cancer biology, etiology, prevention, and treatment. The goals of ICIC are to develop and promote more effective ways of disseminating information among cancer researchers and practicing physicians throughout the world.

A major activity involves production, maintenance, and distribution of the Physician Data Query (PDQ) data base. Updated monthly, the PDQ data base consists of four component files (including cancer information and literature, clinical research protocols, and a directory of physicians and organizations), linked together for user-friendly retrieval through common data elements. The goal of PDQ is to disseminate information on progress in cancer treatment to practicing physicians and to reduce cancer mortality nationwide.

An Editorial Board meets monthly to review and discuss medical issues derived from perusing the literature and attending medical meetings. Over the year, the Editorial Board has edited for clarity many of the tumor statements currently in PDQ. In addition, it has approved revisions to therapeutic options for many tumor statements. An average of 20–25 statements are modified and updated each month.

Most PDQ state-of-the-art statements refer to specific therapies as standard regimens. Standard therapy protocols are designed as a reference for a given regimen. For many of these standard treatments, a full summary of dose schedule and modification has been prepared.

International Cancer Research Data Bank: Established by the National Cancer Act of 1971, the International Cancer Research Data Bank (ICRDB) has developed a comprehensive range of technical information services and products that disseminate cancer research information to scientists and practicing physicians around the world. The major information resources are:

- The online computer data bases of the CANCERLIT, CLINPROT, and PDQ, which enable scientists to retrieve cancer information at more than 10,000 locations within the United States and 13 foreign countries.
- Three series of publications (*Cancergrams, Oncology Overviews,* and *Recent Reviews*) containing abstracts of published cancer research results in special formats designed for easy use and quick reference.

Publications Branch: The Publications Branch coordinates the publication of cancer research findings in NCI's scientific journals and is responsible for developing and implementing procedures that improve the dissemination of published information to the scientific community. There are two monthly publications, *Cancer Treatment Reports* and the *Journal of the National Cancer Institute,* and one nonserial publication, *NCI Monographs.*

Manuscript tracking activities have been consolidated and streamlined in 1987. The computerized tracking system, which uses dBASE III software and IBM hardware, has been fully implemented for all ICIC journals produced in the Publications Branch. As part of this records automation, the review process has been extensively revised and expedited, leading to a decrease in the time between manuscript submission and acceptance. As a result, the journals' scientific articles are published more promptly, facilitating a rapid dissemination of the results of research and treatment of cancer. Statistical reports available from the manuscript tracking system have assisted the Editors-in-Chief to analyze and evaluate the trends in manuscript submissions, reviews, and revisions.

Computer Communications Branch: The Computer Communications Branch maintains and operates the ICIC Computer Communications Center and a local area network in support of NCI's centralized scientific and medical information services. Other activities include:

- Developing and publishing standards and procedures for use of the computer facility and terminal devices linked to it;
- Developing and acquiring systems software and telecommunications to support the computer facility;
- Coordinating all hardware and systems software of the computer center to enhance efficiency; and
- Developing, maintaining, and upgrading by exploiting state-of-the-art technology highly specialized electronic information delivery systems such as CD-ROM (compact disc-read only memory), a new optical storage and distribution medium.

NIH Visiting Program: During FY 1987, NCI hosted a total of 319 foreign scientists from 46 countries who came to the United States to engage in collaborative cancer research activities. Five scientists were appointed as Experts, and 134 came as Guest Researchers, whose financial support was provided by sources other than NCI. These Visiting Sci-

entists worked in the laboratories of cancer treatment, etiology, and biology and diagnosis. These associations have been mutually beneficial. The NCI host scientists were afforded opportunities to learn from the visitors about cancer problems in a given foreign country, about factors peculiar to that nation that might be related to the morbidity and mortality of cancer, and about activities under way toward the management, treatment, and prevention of cancer. Reciprocally, the foreign visitors were provided with unique opportunities to improve their mastery of the scientific method or to develop their potential for scientific contributions to laboratory and clinical research. Such scientific interaction ultimately leads to improved quality of care for cancer patients throughout the world.

Chapter V
National Eye Institute

Introduction

The mission of the National Eye Institute (NEI) is to reduce the prevalence of blindness, visual impairment, and eye disease in the United States and worldwide through basic and applied research and training. The World Health Organization (WHO) estimates that about 28 million of the world's people are blind, the majority of them living in the developing nations of Asia, Latin America, and Africa. In addition, there are untold millions with lesser degrees of visual impairment. At the current level of preventive and curative activities, the world's number of blind people is projected to double by the year 2000 as a result of demographic changes. As global populations increase and their median age rises, more people move into the age brackets affected by cataract, glaucoma, and other age-related ocular diseases. But this need not occur. Well-planned sight conservation programs that employ current medical knowledge and resources could be used to avoid 50 to 80 percent of all blindness. A global effort is needed to increase public and governmental awareness of the problem of blindness, mobilize available resources, promote development of effective programs in countries that now lack them, and increase the effectiveness of programs already in existence.

The specific objective of NEI international activities is to facilitate the development and application of appropriate effective programs by:

- Evaluating available health technologies, promoting the most cost-effective intervention and prevention programs, and encouraging their availability to affected populations, especially in developing countries;
- Conducting collaborative applied research studies aimed at developing preventive methods for dealing with specific eye diseases;
- Conducting controlled clinical evaluations of research findings that appear to be effective; and
- Exchanging information on recent scientific advances and their appropriate application to blindness and visual problems.

Highlights of Recent Scientific Advances Resulting From International Activities

Open-angle glaucoma is a major cause of visual impairment in black populations. The reasons for this are unknown. A recently completed pilot study carried out in Barbados, West Indies, suggests a high glaucoma prevalence. A major followup study is now planned to determine the true prevalence of the disease and to identify risk factors associated with its etiology among the black population.

Cataracts are a leading worldwide cause of blindness and visual disability. About 17 million persons, in both developed and developing countries, have severe visual loss from cataracts; each year an additional 1.25 million around the globe are affected. By far the most common of the many different kinds of cataracts is age-related cataract. Many people are robbed prematurely of productive potential and are functionally impaired needlessly. The potential for preventing, or at least delaying, onset of age-related cataract depends upon identifying the factors leading to cataract development. NEI is sponsoring case-control studies in the United States, Italy, and India of possible personal and environmental risk factors including diet, biochemical status, systemic disease history, and environmental exposure to sunlight and drugs. Country comparisons are expected to provide leads to why the onset of cataract occurs at earlier ages in some geographic areas than in others and to help design interventions that may delay progression.

"At least a third of all blind people in the world could have effective sight restored by cataract operations," according to Sir John Wilson, Senior Consultant, In-

ternational Initiative Against Avoidable Disablement. This unnecessary blindness continues more because of a problem of delivery of services than of technology. In collaboration with the Pan American Association of Ophthalmology (PAAO) and Helen Keller International, operations research techniques to solve these problems were applied by demonstration projects conducted in Chimbote, Peru, and Campinas, Brazil. The projects attempted to create zones free of operable cataract blindness. Deterrents to achieving this goal are being identified, and the lessons that have been learned are being evaluated for their applicability throughout Latin America and other parts of the world for program planning to reduce the backlog of cataract blindness.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

China: The Director of the Zhongshan Ophthalmic Center, Zhongshan Medical College, and the Director of NEI signed an Institute-to-Institute Memorandum of Understanding. This agreement on a collaborative program of research had been emerging since the talks began in 1984. The Zhongshan Center is the first such unit to receive official designation as an ophthalmic research center by the Chinese Government. Since the initial visit, the two institutions have exchanged scientists, participated in workshops and conferences, and developed collaborative research protocols—some of which are ready to be implemented. The Chinese Government also recently established the Peking Union Medical College (formerly Capital Medical Hospital) as an ophthalmic research center. This center is in the early stages of strengthening its scientific program and scientists are being trained and exchanged with NEI. With collaboration from the WHO Prevention of Blindness Program, a joint research project to study the prevalence of cataract and maculopathy in Tibet was conducted. Followup studies are being planned.

India: *Vitamin A Deficiency:* Vitamin A deficiency (xerophthalmia) is the leading cause of blindness and nutrition-related visual impairment among children worldwide. In India alone, it is said to account for 180,000 cases annually. An estimated 20,000 children become blind annually from nutritional deficiencies, primarily deficiency of vitamin A; half of these children die within a year. A basic and applied research program to understand and attack this problem is operational at the Clinical Research Center for the Prevention of Nutritional Blindness, established in 1982 in collaboration with the National Institute of Nutrition in Hyderabad, India. The Clinical Research Center uses U.S. and Indian research facilities in an applied clinical research program. The program seeks to identify children who are at great risk of becoming blind from hypovitaminosis A and other concurrent factors, to determine practical ways to prevent this blinding condition, and to develop more cost-effective programs that provide vitamin A prophylaxis to populations at the highest risk.

A community-based study of measles, ocular disease, and vitamin A status has been completed and the results published (*American Journal of Clinical Nutrition* 1986;44:924). The project was conducted among more than 1,500 children less than 6 years old in a community setting. Morbidity was monitored weekly through two seasons of measles in which about 400 cases occurred. This permitted a parallel study of morbidity patterns among mildly vitamin A-deficient populations, whether or not they contracted measles, and allowed for a comparison with similar studies reported from Indonesia. The Indonesian studies suggested an increased risk of respiratory disease and diarrhea among mildly vitamin A-deficient children.

More than 1,500 preschool urban Indian children were followed weekly for 12 to 18 months for morbidity, and ophthalmic examinations were conducted initially and at 6 and 12 months. Children with mild xerophthalmia (Bitot's spots and night blindness) at the start of a 6-month interval developed respiratory disease in the interval twice as often as children with normal eyes at the start of the interval. In contrast to the Indonesian studies, no association was found between mild xerophthalmia and the incidence of diarrhea. These studies emphasize the important association between frequent systemic infections and a deteriorating vitamin A status.

Additional studies were conducted on the conjunctival epithelium of subsets of children who were clinically normal, clinically vitamin A deficient, and clinically vitamin A deficient with measles. The latter group was further divided into those with low or normal serum levels of vitamin A. Vitamin A deficiency sufficient to cause clinical signs without subephithelial scarring or keratinization was associated with hyperproliferation of the conjunctiva, whether or not there was a superimposed measles infection. There was no association between protein-energy nutritional status and corneal lesions, but vitamin A therapy was useful in most cases in reversing the progression of the corneal involvement.

The results from the above studies emphasize the importance of vaccination programs against measles and the therapeutic use of high doses of vitamin A during the acute phase of the disease among high-risk groups of Indian children. Furthermore, the data suggest that vitamin A prophylaxis to marginally deficient children also may contribute to decreased morbidity from infections other than measles.

Marginal vitamin A deficiency is not easily assessed by relatively noninvasive methods. New approaches to the assessment of subclinical deficiency are being pursued at the clinical research center. One such approach using a small oral challenge of vitamin A (relative dose-response test) was successful in identifying such cases when applied among mildly to moderately malnourished Indian children. A new study is exploring the reliability of another simple approach that depends upon the microscopic evaluation of the conjunctival epithelium content of goblet cells evaluated by filter paper exfoliate cytology. Other nutritional factors that may confound the reliability of the results are being studied, including the rapidity of return to normal following vitamin A enhancement of a typical diet.

Some children in an area, even in the same household, develop clinical vitamin A deficiency; others do not. Another study is nearly completed in which the risk factors in the development of xerophthalmia are studied among age- and sex-matched controls with the hope of identifying factors that might be altered to prevent the condition from occurring.

Keratomalacia, or liquefaction of the cornea, is an irreversible consequence of severe vitamin A deficiency combined with other factors. A recently completed study has shown that the proteolytic enzyme collagenase is elevated in the tears of children with keratomalacia and may be directly implicated in the liquefaction process that frequently occurs in the disease. Results of this study on more than 60 cases and controls are expected to provide guidance for potential interventions for more effective treatment and control of this disease.

NEI and the Indian Council of Medical Research (ICMR) developed a collaborative program of blindness research under the 1983 Indo-U.S. Science and Technology Initiative. The projects are supported primarily by funds from the Indian Government through ICMR and from the U.S. Government through the National Science Foundation and NEI. In addition to some of the vitamin A projects already noted, this initiative includes projects to reduce blindness in India from other causes, specifically cataract and Eales' disease.

India has had an effective mass cataract intervention program, and NEI is engaged in collaborative research in an effort to make this program even more effective. The following studies are in progress.

Hospital-Based Case-Control Study of Risk Factors for Age-Related Cataract: The study, conducted at the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, will be completed in 1988. It is designed to seek risk factors that may be associated with the development of age-related cataract, emphasizing nutritional parameters such as diet and biochemical status and environmental parameters such as exposure to sunlight and drugs. Unlike previous epidemiologic studies of this kind, this study places a heavy emphasis on biochemical evaluations among cases and matched controls. More than 1,000 cases and controls have been enrolled to date, and more than 800 blood samples have been analyzed in Indian laboratories. Results from this study will be compared to those from similar studies being conducted in the U.S. and Italy.

Operational Research to Reduce Barriers to Cataract Surgery: This study is being conducted in Madurai in collaboration with the Aravind Eye Hospital and the University of Michigan. U.S. and Indian scientists with expertise in operations research, health education, and epidemiology have joined hands to field-test and evaluate alternatives in overcoming social, economic, and logistic barriers to cataract surgery among the rural blind in India. Four educational and motivational activities aimed at increasing both awareness and acceptance of cataract surgery are being evaluated in a probability sample of 100 villages. These activities are:

- House-to-house visits by successfully operated cataract patients;
- House-to-house visits by a basic eye-health worker;
- Visits by a screening van at a central location in a village; and
- Health education campaigns carried out at weekly marketplaces.

To determine the effect of economic subsidies on surgical acceptance rates, each of these four activities is being tested with two different combinations of incentives: free travel, food, surgery, and eyeglasses are offered to half the study subjects; free surgery and eyeglasses only are offered to the other half. The final evaluation phase of the study will be complete by the end of 1987. Results from this study and from those obtained in studies conducted in Peru and Brazil are expected to provide information needed to design more effective programs to reduce the cataract prevalence worldwide.

Acquisition and Allocation of Brunescent and Other Cataracts: The study is being conducted by Oakland University, Rochester, Michigan, in collaboration with ophthalmic surgeons and biochemists in India. American cataract researchers have been hampered by the lack of cataractous lenses on which to conduct biochemical and other studies because surgical removal procedures in the United States destroy the lens. In India, cataracts are removed by procedures that leave the lens intact. An arrangement has been made to collaborate in studies on lenses available in India using biochemical, biophysical, and other techniques. The arrangement includes training Indian technicians in the use of the camera and the classification system used by the Cooperative Cataract Research Group.

Laboratory and Clinical Studies of Eales' Disease: This study is being conducted in Madurai in collaboration with the Madurai Kamaraj University, Department of Immunology, and the Aravind Eye Hospital. The clinical part of the study was started in April 1984. More than 50 patients and a similar number of controls have been studied both clinically and in the laboratory. It is too soon to evaluate the effectiveness of the treatment regime. The laboratory studies are revealing some differences that require followup to determine whether they are associated with the etiology of the disease. Of the several different immunological factors studied, the most promising is a specific protein isolated from the blood of cases but not controls. Studies are under way to purify and characterize this protein in preparation for future studies to determine its etiologic relationship to the disease.

In addition to these research projects, NEI scientists and consultants in biostatistics, biochemistry, nutrition, and clinical ophthalmology continued their collaboration with Indian Government officials on blindness prevention programs.

Italy: On March 12, 1985, NEI and the Italian Ministry of Health signed an agreement in vision research. This agreement encourages cooperation in research, including biochemical, genetic, clinical, and epidemiologic approaches. Two projects were selected for this inaugural effort. One is a genetic study of retinitis pigmentosa, which is particularly prevalent in Sardinia, giving special attention to the recessively inherited form of the disease and a case-control study of risk factors in age-related cataract.

The other is a collaborative U.S.-Italian case-control study of age-related cataract, which was started in September 1986. Although investigators from the University of Parma are conducting this study, both U.S. and Italian scientists are involved. The data-collecting center is located at the National Institute of Health in Rome. The objectives of the study are to identify risk factors for age-related cataract, evaluate methods of *in vivo* cataract classification, and compare the findings with those of parallel studies being conducted in the United States and India.

The pilot phase is completed, and phase II of the study is well under way; it is expected to last 2 years. During this phase, data will be collected by interview, ocular examination, ocular photography, and laboratory analysis of blood specimens. During Phase III, the last 6 months of the study, data will be analyzed and manuscripts prepared.

Japan: NEI and the Japan Society for the Promotion of Science, recognizing the contributions that vision research scientists can make to the prevention, diagnosis, and treatment of diseases of the eye and visual system in the two countries and wishing to foster closer cooperation in this endeavor, have agreed to carry out a scientist exchange program. The two countries have agreed to exchange two scientists from each country annually to conduct joint research, give lectures, and participate in seminars at the host institution. This program has been active since 1977.

The two U.S. scientists who went for short visits to Japan were the Deputy Clinical Director, NEI, and a professor of physiological optics from the University of Michigan. The former pursued research related to ocular inflammation and basic mechanisms of Voyt-Koyanagi-Harada's disease at the University of Tokyo and Kyoto Prefectural University. The latter studied similarities and differences in the spectral distribution of absorption coefficiences of rhodopsin in oriental and occidental eyes at Jikei University, Tokyo.

Two Japanese scientists also came to the United States. A researcher from the Department of Ophthalmology, Hokkaido University, is conducting immunological studies on experimental autoimmune uveitis at NEI. A professor of ophthalmology from Nihon University is on a short-term visit to Johns Hopkins and the universities of Illinois and Wisconsin to study the early treatment of disciform macular degeneration with krypton laser. Using contralateral eyes with disciform macular degeneration, drusen and other macular pathologies will also be studied.

Latin America: Two demonstration projects to create cataract-free zones, one each in Peru and Brazil, are in the final stage of completion. The goal of the projects is to demonstrate a replicable cost-effective means to ascertain and clear the cataract backlog in

a Latin American urban area using the techniques of house-to-house visual acuity screening, outpatient surgery, and in-home community followup. Helen Keller International is sponsoring these projects, which are an outgrowth of efforts initiated by PAAO, NEI, and the Fogarty International Center (FIC) with NEI serving in a consultant role.

West Indies: A major epidemiologic investigation of the prevalence and risk factors in open-angle glaucoma among blacks in Barbados is being planned following a successful pilot feasibility study. In Barbados, open-angle glaucoma is the major cause of blindness, presenting early and associated with advanced visual loss. This NEI-supported study will be conducted by investigators from the State University of New York at Stony Brook and the Queen Elizabeth Hospital in Barbados. Findings from the comprehensive evaluation of risk factors that will be investigated are expected to provide important data for blindness prevention and control programs, particularly those aimed at high-risk black populations.

Activities With International and Multinational Organizations

In FY 1987, NEI continued its activities as a WHO Collaborating Center for the Prevention of Blindness, and the NEI Director continued to serve as a member of WHO's Special Advisory Panel in the Program for the Prevention of Blindness. Other NEI staff provided consultative assistance to the WHO program on request.

Over the past year, the WHO Program for the Prevention of Blindness, which continues to be partially supported by contract with NEI, initiated several new projects in African, Southeast Asian, and Western Pacific regions. With the assistance of the WHO Collaborating Center at Jutendo University School of Medicine in Tokyo and NEI, the Peking Union Medical College in Beijing, China, carried out a prevalence study of age-related cataract in Tibet. The survey has been completed, and the data are being analyzed. Field-testing of the French translation of the new WHO Eye Examination Form was completed in Togo, and a second test will soon be implemented in the People's Republic of Congo. The Aravind Eye Hospital in Madurai, South India, will provide the site for a study of the efficacy and cost-effectiveness of the use of vanadium stainless steel sutures in cataract surgery. Other studies of the protective effect of measles immunization on childhood blindness, and development of health education strategies in the control of xerophthalmia, are in the planning stages.

A meeting jointly sponsored by the Pan American Association of Ophthalmology, NEI, and the FIC, held at the NIH in 1986 to discuss the concept of "cataract-free zones," led to the development of two demonstration projects using the principles of operations research. The projects were carried out in 1987 in defined urban areas within a limited population in two Latin American countries, Brazil and Peru. Lessons learned from these projects are expected to assist in developing more effective intervention strategies for reducing the prevalence of cataract blindness among underprivileged communities.

NEI continues to work closely with Helen Keller International and other voluntary organizations in designing service and research programs to reduce the problem of blindness, of whatever etiology, wherever it occurs worldwide.

Extramural Programs

In FY 1987, NEI made 20 awards to foreign institutions in eight countries. Outstanding research and training projects were supported in the following major research categories: retinal and choroidal diseases; corneal diseases; cataract, glaucoma, and strabismus; amblyopia; and visual processing. Both basic and clinical research projects were included. Some examples follow.

Scientists at the University of Sydney in Australia are investigating how normal lens forms and how developmental processes are involved in the maintenance of its normal structure and function throughout life. Information from these studies is basic to understanding developmental and growth abnormalities, and perhaps even the more insidious aging changes that may lead to cataract.

Scientists in England are studying the structural organization of collagen, proteoglycans and glycoproteins in normal human corneas, and the changes that occur in certain pathologic conditions such as macular corneal dystrophy.

At the Peking Union Medical College Hospital, Beijing, Chinese researchers are pursuing studies of the biochemical mechanisms by which the hyperglycemia of diabetes mellitus causes reduction in pericyte viability. The loss of pericytes may impair the integrity of the retinal microvasculature, leading to the breakdown of the blood-ocular barrier and resulting in diabetic retinopathy.

The Ontario Cancer Institute in Toronto serves as the coordinating center for the multicenter Collaborative Ocular Melanoma Study. This study, conducted at cooperating clinics located throughout the United States, is a controlled clinical trial to com-

pare the efficacy of enucleation with irradiation in the treatment of eyes with choroidal melanoma.

NEI was represented and presented papers at the following international meetings:

- International Congress on Cataract, International Association for Cataract Related Research, Palermo, Italy, October 14–31, 1986;
- International Symposium on Polyol Pathway and Its Role in Diabetic Complications, Nagoya, Japan, October 28–30, 1986;
- Third General Assembly, International Agency for the Prevention of Blindness, New Delhi, India, December 6–11, 1986;
- Pan American Congress of Ophthalmology, Santa Domingo, Dominican Republic, April 5–10, 1987;
- Third World Congress on Cornea, Washington, D.C., April 27–May 1, 1987;
- International Council of Ophthalmology, Barcelona, Spain, May 22, 1987;
- Asia Pacific Academy of Ophthalmology, Kuala Lumpur, Malaysia, June 7–12, 1987;
- International Association for Cataract Related Research, Third International Congress, Genoa, Italy, September 4–6, 1987; and
- International Symposium on Elevated Dosages of Vitamins, Interlaken, Switzerland, September 7–9, 1987.

Intramural Programs and Activities

NEI continues to serve as an international center for research and training in eye disease. In FY 1987, 19 Visiting Fellows, 7 Visiting Scientists, 20 Visiting Associates, 11 Guest Researchers, and 11 other special volunteers and investigators from 18 countries conducted research studies in NEI's Bethesda facilities. Their work included basic laboratory investigations in the molecular structure and development of the visual system, sensory and motor disorders of vision, and the biochemical bases of retinal and corneal disease and cataract development. In addition, Visiting Scientists collaborated with NEI investigators in clinical studies to define, treat, and prevent such disorders of vision as genetic and development defects, ocular inflammatory disease, and ocular complications of systemic conditions such as diabetes.

One Visiting Fellow from the Peking Union Medical College Hospital, Beijing, working in the Section on Cataract, has studied hereditary cataracts that occur in guinea pigs. The work has uncovered and extensively characterized a novel lens protein that appears to be unique to the guinea pig. Evidence has been obtained that a mutation in the gene for this particular protein may be the primary defect responsible for this cataract. Results from these studies may lead to exciting new avenues of research into the evolution and function of the structural proteins of the lens as well as the mechanisms responsible for inherited cataract.

Chapter VI
National Heart, Lung, and Blood Institute

Introduction

Heart, lung, and blood diseases and resources continue to present major national and international challenges. Although death rates from cardiovascular diseases in the United States have declined, they remain the number one cause of death, disability and economic loss in our country (Figure VI–1). The economic toll in the United States from heart, lung, and blood diseases is estimated at $100 billion a year, making prevention and control of these diseases a high national priority. Also, World Health Organization (WHO) data show that cardiovascular diseases are the "topmost public health killers throughout the world." The marked national differences in cardiovascular and pulmonary disease death rates (Figure VI–2) and trends (Figure VI–3) raise scientific questions of importance to the U.S. and international scientific communities and emphasize the need for cooperation to understand the reasons for these differences.

During FY 1987 the National Heart, Lung, and Blood Institute (NHLBI) continued to expand international cooperation in selected areas of mutual interest and benefit relating directly to the priorities in the National Heart, Blood Vessel, Lung, and Blood Program mandated by the President and Congress. They are integrated within the Institute's national programs to reduce 4 of the 10 leading causes of death in the United States.

This year, NHLBI celebrated its 40th anniversary and also participated in the centennial celebration of the National Institutes of Health. It was noted that international cooperation and exchange of information have been important features of NHLBI programs since their inception. NHLBI's international programs are designed to augment national research efforts in virtually all priority research areas designated in the National Heart, Blood Vessel, Lung, and Blood Program Plan. Currently, the Institute participates in collaborative research with more than 20 nations. By sharing the resources of the U.S. biomedical research community with those of other nations, scientists are able to obtain a broader understanding of disease processes, modes of diagnosis and treatment, and methods of prevention. International collaboration also extends opportunities to advance understanding of how environmental and genetic factors influence the risk of cardiovascular and pulmonary disease among diverse populations. Table VI–I summarizes the entire spectrum of the national research program and identifies how the international programs intersect with these activities.

Highlights of Recent Scientific Advances Resulting From International Activities

Described below are three highlights from NHLBI international scientific developments reported in FY 1987.

Epidemiologic Studies of Cardiovascular Disease

Scientific cooperation with several countries continues to emphasize epidemiologic studies that compare the trends and rates of disease and risk factors to understand the overall disease process and predictors of disease. During FY 1987, new information was derived from studies with China and Japan. Preliminary analyses of data collected in China during 1981–87 and comparisons of these data with data from U.S. populations show significant differences, raising important scientific questions to be explored in further joint research. For example:

- For both Chinese men and women, mean blood pressure and the prevalence rate of hypertension for workers and farmers were significantly lower in the South than in the North;
- The mean serum total cholesterol for each of four sex-occupation groups was lower in the South than

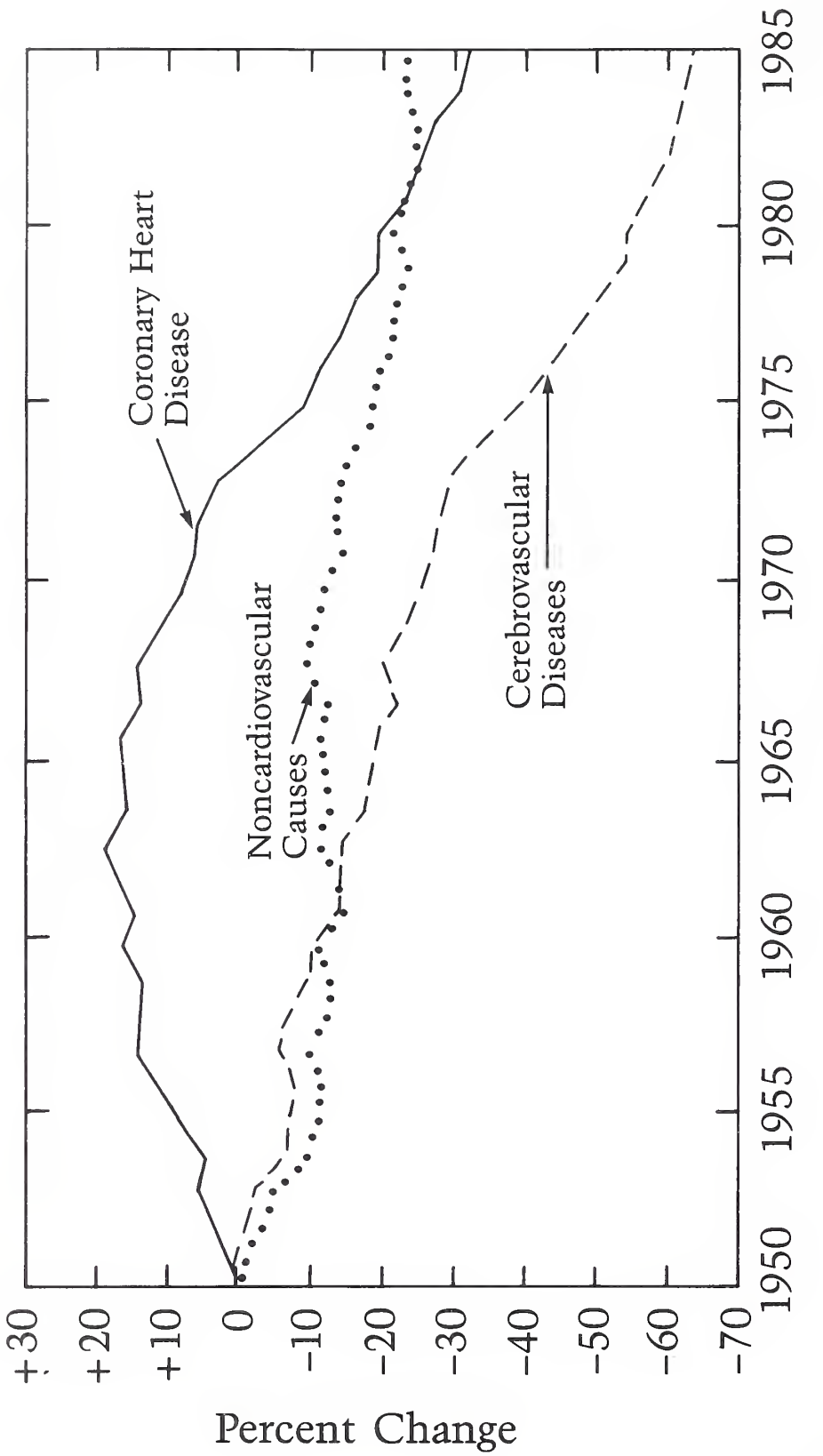


Figure VI–1. Percent change in age-adjusted death rates for coronary heart disease, cerebrovascular diseases, and noncardiovascular causes of death; United States, 1950–85

Source: Vital Statistics of the United States, National Center for Health Statistics.

Figure VI–2a. Death rate for all causes and cardiovascular diseases, men ages 35–74 in selected countries, 1982

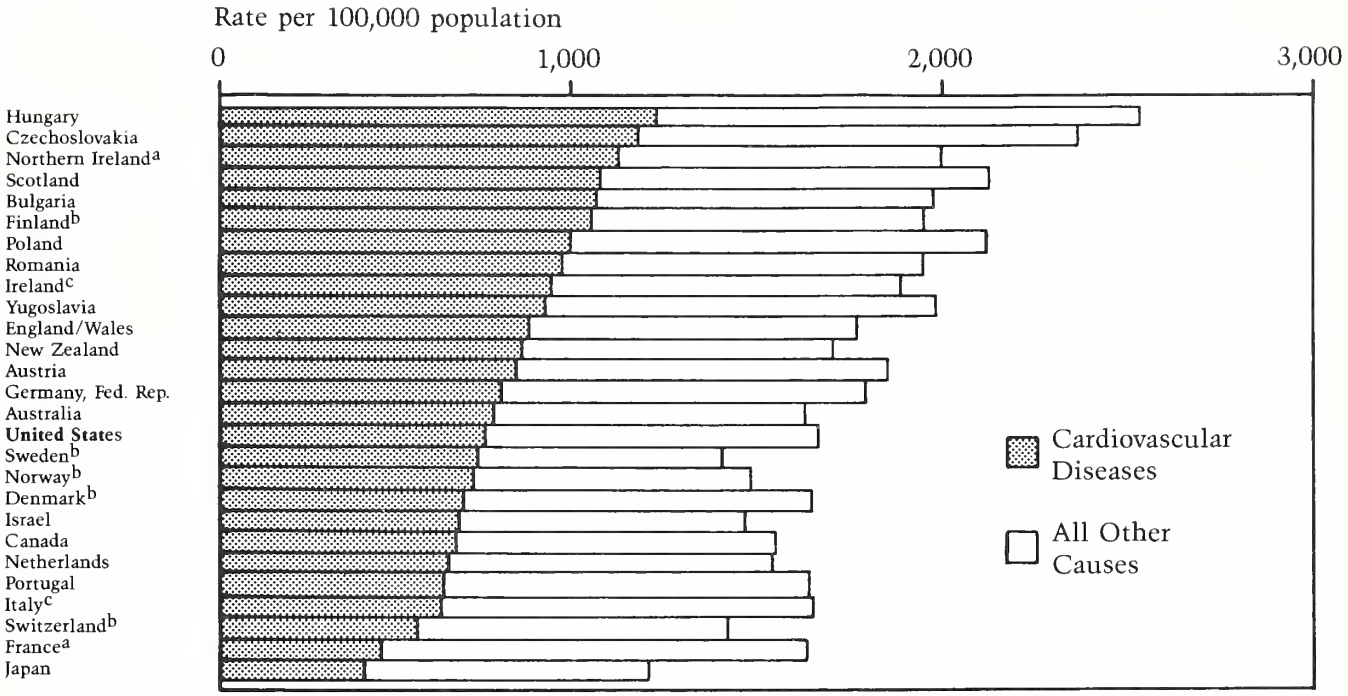
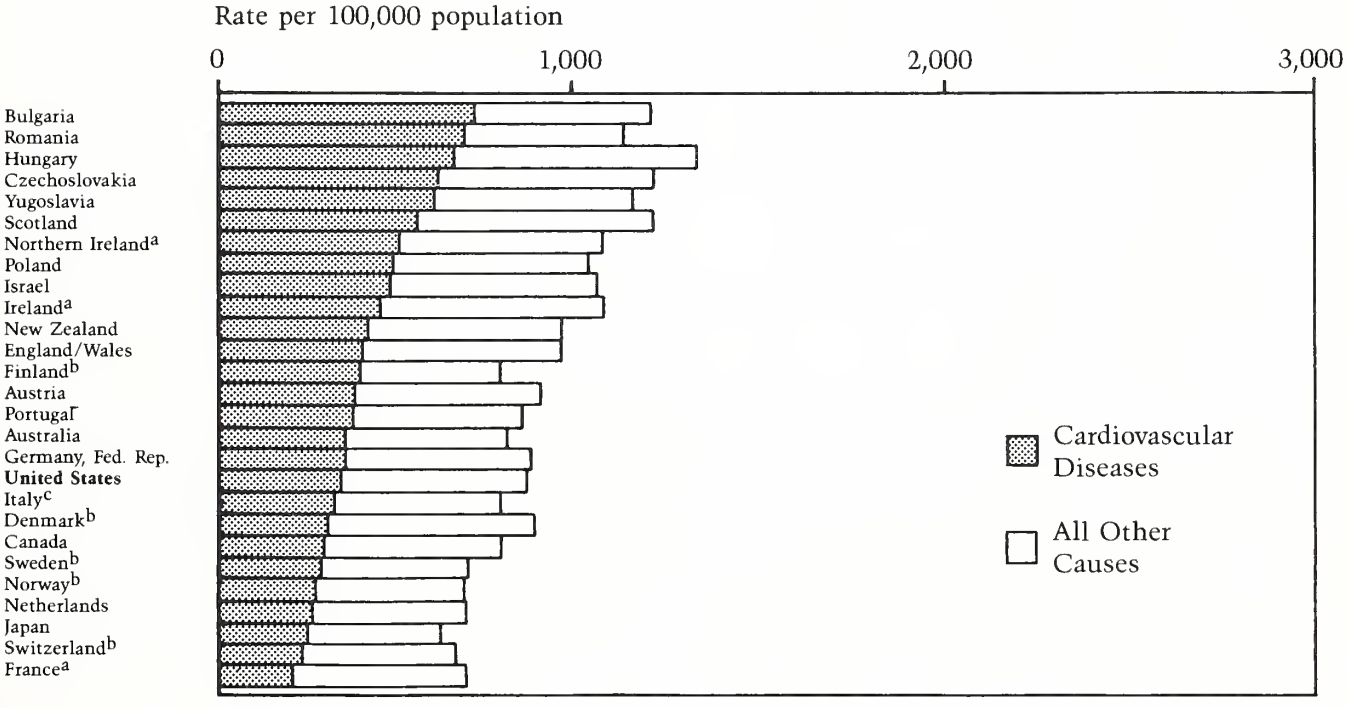


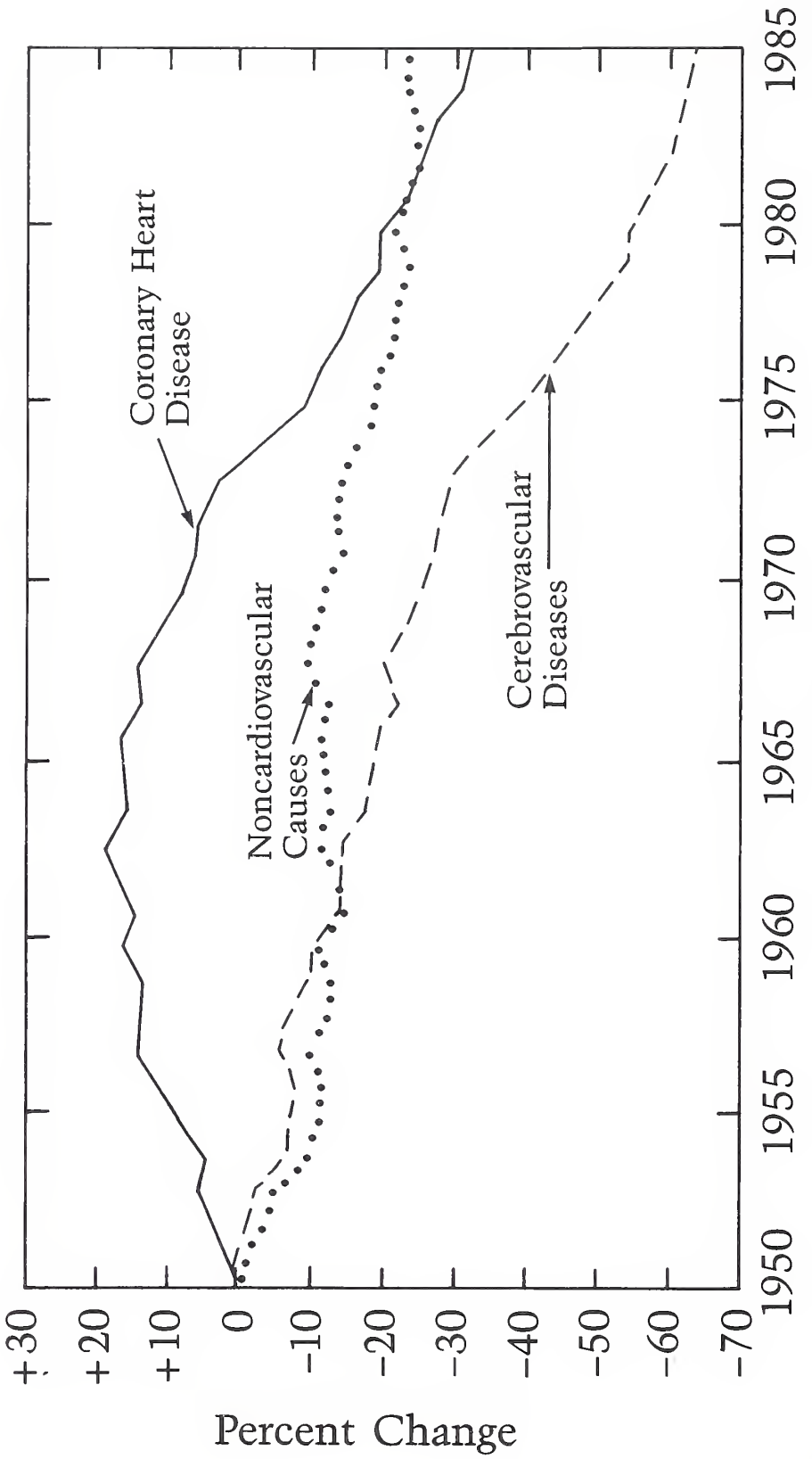
Figure VI–2b. Death rate for all causes and cardiovascular diseases, women ages 35–74 in selected countries, 1982



Source: World Health Organization.

[a]1981.
[b]ICD/8 390–458 for cardiovascular disease.
[c]1980.
Note: ICD/9 390–459 for cardiovascular disease except as noted. Rates are age-averaged.

Figure VI–1. Percent change in age-adjusted death rates for coronary heart disease, cerebrovascular diseases, and noncardiovascular causes of death; United States, 1950–85



Source: Vital Statistics of the United States, National Center for Health Statistics.

Figure VI–2a. Death rate for all causes and cardiovascular diseases, men ages 35–74 in selected countries, 1982

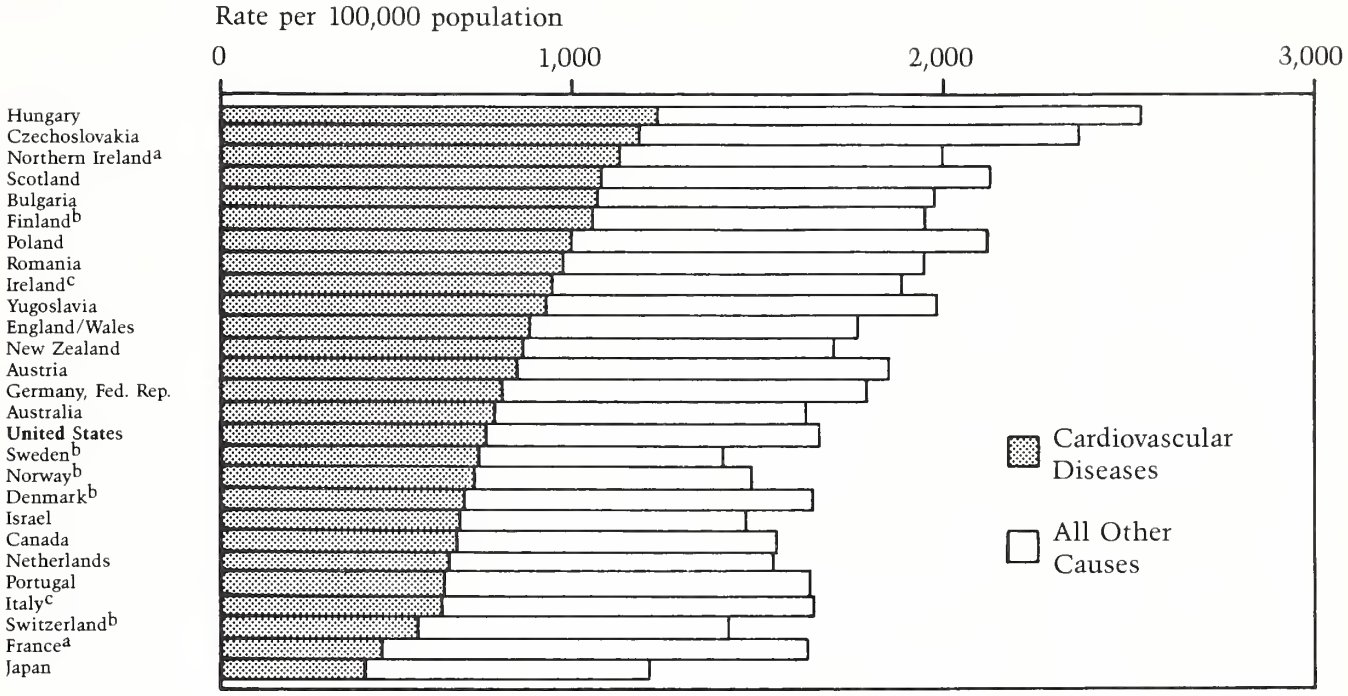
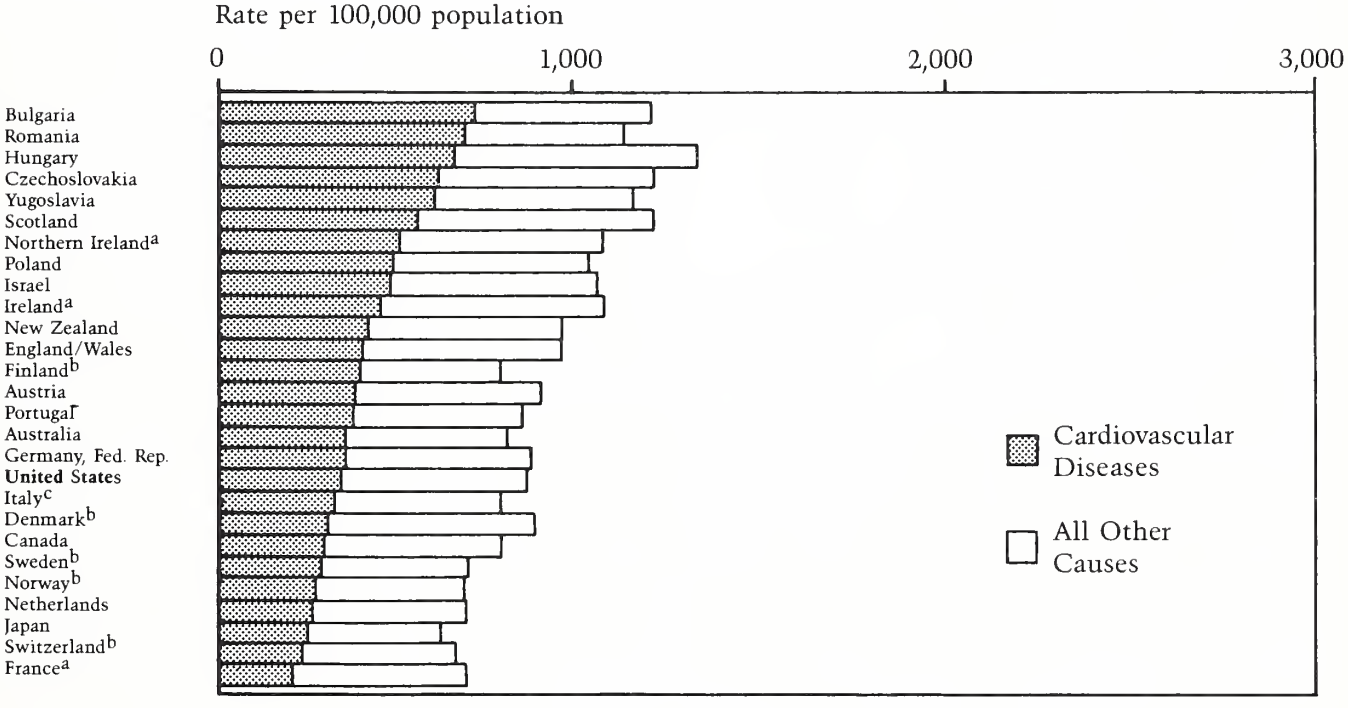


Figure VI–2b. Death rate for all causes and cardiovascular diseases, women ages 35–74 in selected countries, 1982



Source: World Health Organization.

[a]1981.
[b]ICD/8 390–458 for cardiovascular disease.
[c]1980.
Note: ICD/9 390–459 for cardiovascular disease except as noted. Rates are age-averaged.

Figure VI–3a. Percent change in the death rate for cardiovascular disease, men ages 45-54 in selected countries, 1970-82[a]

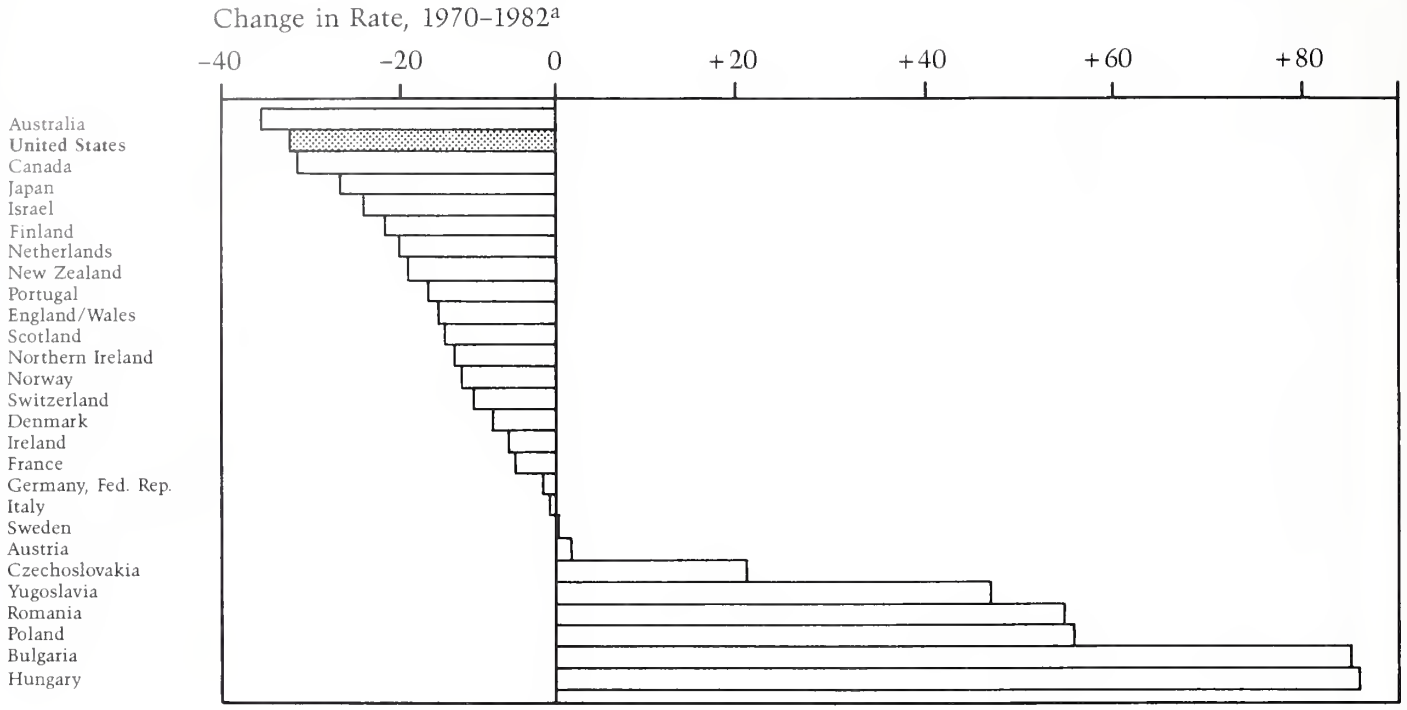
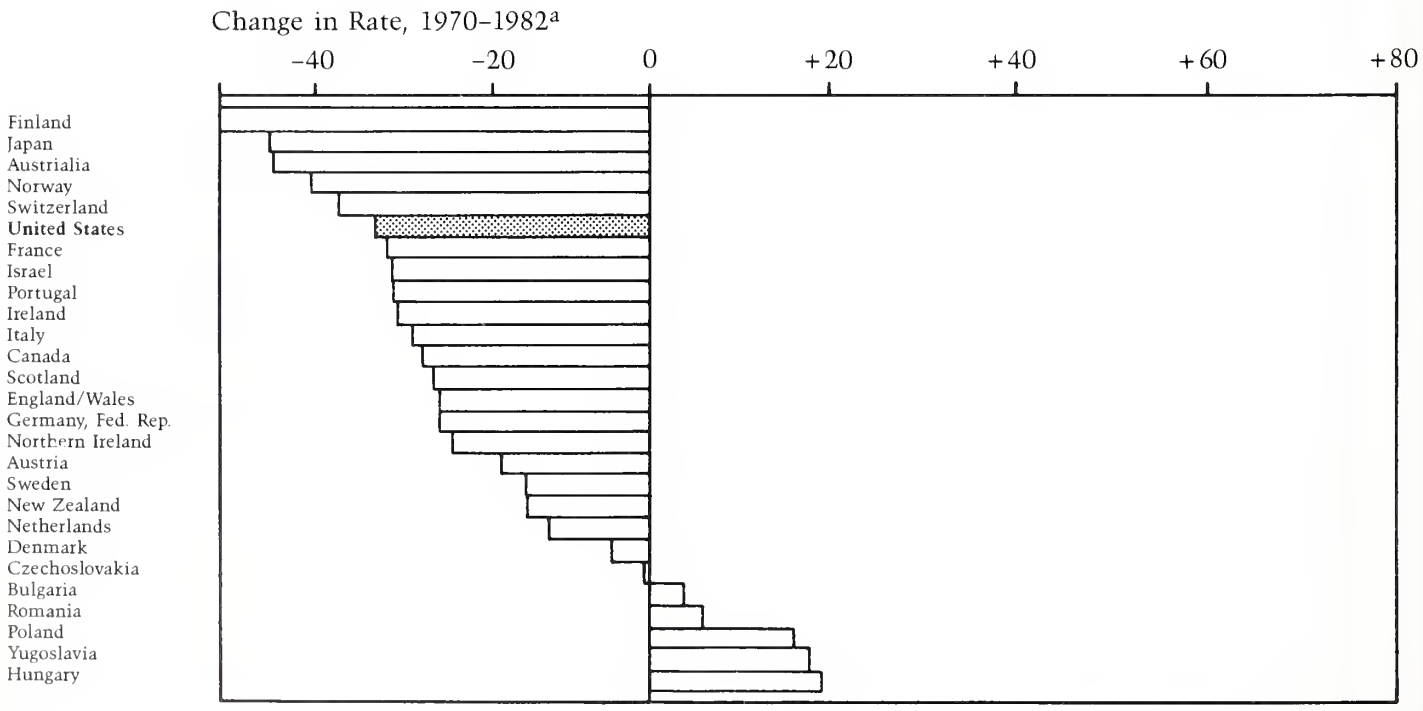


Figure VI–3b. Percent change in the death rate for cardiovascular disease, women ages 45-54 in selected countries, 1970-82[a]



[a]For five countries the change is only to 1980 or 1981.

Source: World Health Organization.

Table VI–1

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE INTERNATIONAL PROGRAMS, FY 1987

	Arteriosclerosis	Hypertension	Cerebrovascular Disease	Coronary Heart Disease	Peripheral Vascular Diseases	Arrhythmias	Heart Failure and Shock	Congenital and Rheumatic Heart Disease	Cardiomyopathies and Infections of the Heart	Circulatory Assistance	Structure and Function of the Lung	Chronic Obstructive Pulmonary Diseases	Pediatric Pulmonary Disease	Occupational and Immunologic Lung Dis.	Respiratory Failure	Pulmonary Vascular Diseases	Bleeding and Clotting Disorders	Disorders of the Red Blood Cell	Sickle Cell Disorders	Blood Resources
Argentina		●						●												
Brazil						●			●			●							●	
Canada				●		●						●	●		●					
China	●	●	●	●								●		●						
Czechoslovakia	●	●		●								●		●			●	●		
France		●								●	●			●		●				
Germany, Fed. Rep.	●	●	●	●								●		●			●			
Greece																		●		
Hungary				●		●		●									●			●
India																				
Israel	●	●	●					●									●			●
Italy	●	●		●																
Japan	●	●	●	●								●								
Korea																				
Mexico	●	●																		
Nigeria														●						
Pakistan		●		●																
Poland	●	●		●		●			●			●								
Spain	●	●		●										●		●				
Thailand																	●			
Turkey	●																			
U.S.S.R.	●	●		●		●	●	●		●	●	●		●	●	●	●			●
Venezuela						●	●		●											
Yugoslavia	●	●		●						●										
Taiwan		●																		

in the North (the cholesterol levels of all Chinese populations were significantly lower than those found in the U.S. populations studied); and

- The serum HDL cholesterol levels were higher for Chinese men than for U.S. men.

Cooperation with Japan continues to focus on hypertension and atherosclerosis. Several findings from the joint studies deserve attention. Both the United States and Japan share a high prevalence of hypertension, yet its outcome differs significantly between the two nations. In Japan, stroke is the more common outcome of hypertension, whereas in the United States, heart attack is more usual. U.S. and Japanese scientists are exploring cardiovascular risk factors through pathoepidemiologic studies. Atherosclerosis is being measured in pathological specimens collected and analyzed in both countries via carefully standardized techniques. These studies show that the prevalence of atherosclerotic lesions in the coronary artery and abdominal aorta of a population studied in the United States was three times higher than in the Japanese cohort. Other joint analyses show that although the Japanese diet is becoming more western and presumably more atherogenic, ischemic heart disease rates are declining in Japan. This raises fundamental questions that scientists hope to address in future cooperation.

Basic Research on Heart and Lung Cells

During the Joint U.S.-U.S.S.R. Symposium on Heart and Lung Metabolism in September 1987, American and Soviet scientists reported on recent joint research reflecting a broad range of approaches to basic research in cardiovascular biology and medicine and pulmonary biology and medicine. The sessions focused on new research findings on the structure and injury of the heart and vascular wall and on signal transduction in heart and lung cells. In the pulmonary area, three topics are receiving particular attention:

- Lung cell biology, including both vascular endothelial and airway epithelial cells;
- Biochemistry of lung cell receptors and transmembrane signaling; and
- Pulmonary hypertension and asthma.

In the cardiovascular area, both sides emphasized the need to continue to develop the following research technology for the joint studies:

- Structure/function relationships of proteins serving as receptors, ion channels, and other signaling proteins in heart and vascular cells using recombinant DNA technology, site-directed mutagenesis, and other techniques of molecular biology; and
- Control of expression of genes for receptors, ion channels, signaling proteins, and cytoskeletal and extracellular matrix proteins in the heart and vascular system.

Pulmonary Aspects of Acquired Immunodeficiency Syndrome (AIDS)

Joint research activities under way with France and the Federal Republic of Germany (FRG) include studies of the pulmonary complications of human immunodeficiency virus (HIV) infection. This cooperation is part of a multinational research effort by the NHLBI to collect information on pulmonary complications caused by HIV infections among various risk groups and determine the types, incidence, course, and outcome of pulmonary disorders in recently diagnosed patients with AIDS, in recently diagnosed (3 to 6 weeks) patients with AIDS-related complex, and in individuals asymptomatically infected with AIDS.

Summary of International Programs and Activities

The Institute's international programs and activities are carried out within the mandates of the National Heart, Blood Vessel, Lung, and Blood Program. The direct costs for NHLBI international activities for FY 1987 are summarized in Table VI-2.

Bilateral Agreements and Other Country-to-Country Activities

Argentina: The U.S.-Argentina agreement is pending ratification by Argentine authorities, and Argentina is reviewing proposals in biomedical research.

Brazil: In July 1987, a meeting was held of the newly formed U.S.-Brazil Presidential Panel on Science and Technology. The panel identified priority areas of mutual interest and benefit, including:

- Epidemiology of arteriosclerotic and hypertensive disease;
- Cardiomyopathies, including Chagas' disease;
- Fibrotic lung disease; and
- Genetic variability related to sickle cell disease.

Canada: A major mission of NHLBI is to validate new and improved treatment modalities of heart,

Table VI–2

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE INTERNATIONAL PROGRAMS, DIRECT COSTS, FY 1987

	Number	Countries	Funds Paid (in dollars)
Fellowships	8	Australia Sweden United Kingdom	161,772
Contracts	13	Belgium Canada Sweden WHO International Study	3,515,777
Grants	28	Australia Canada China Germany, Fed. Rep. Israel Italy Romania Sweden Thailand United Kingdom	2,020,941
Total Awards	49		5,698,490
Bilateral Agreements[a]	11	Funds expended in United States[b]	462,345

[a]Collaborating countries pay for costs in their own country.
[b]Activities paid for by NHLBI.

lung, and blood diseases. This entails large-scale, expensive clinical trials that require large patient populations. There has been longstanding cooperation between U.S. and Canadian researchers in clinical trials through the use of jointly developed protocols and standardized methodologies of data collection and analysis. Such cooperation reduces the cost to each country and makes it possible to undertake studies too expensive or too wide-ranging for any one country to sponsor alone. During FY 1987, Canadian researchers cooperated in five NHLBI studies.

Lipid Research Clinic Followup Studies: These studies assess potential adverse effects associated with the ingestion for 10 years or more of the lipid-lowering drug cholestyramine in patients who were 30 years or older at entry into the Coronary Primary Prevention Trial. The health status of these patients is being associated with serum lipid levels, serum lipoprotein levels, and other baseline characteristics measured at entry into the study. One Canadian center is participating in this 12-center trial.

Cardiac Arrhythmia Suppression Trial: This clinical trial, consisting of 21 U.S. centers, 3 Canadian centers, and 1 Swedish center, is testing whether suppression of asymptomatic ventricular arrhythmias in postmyocardial infarction patients results in a reduction in death from arrhythmia.

Studies of Left Ventricular Dysfunction: Cardiac failure remains a major and growing public health problem. Approximately 2 million Americans are affected. The prevalence of congestive heart failure increases with age; therefore, improvements in the average life expectancy are expected to increase the magnitude of this problem in the future. The mortality of these patients is 10 to 20 percent a year. Two randomized, double-blind, controlled trials are under way to address this problem. One Belgian and two Canadian centers are participating with 20 U.S. centers in these clinical trials.

Early Intervention for Chronic Obstructive Pulmonary Disease: This study is under way in one Canadian and nine U.S. centers. It is determining the effect on rate of decline in pulmonary function of "special care" compared with referral to "usual care" in a population of smokers identified as having mild abnormalities in pulmonary function. Special care includes presentation to the smoker of his or her mild abnormality in pulmonary function, smoking cessation counseling, bronchodilator administration, and diligent followup.

High-Frequency Ventilation (HFV) in Premature Infants: This trial is evaluating whether a new type of ventilator that operates at very high frequencies is superior to standard mechanical ventilation in providing ventilatory support to premature infants. Some 20 percent of premature infants who require mechanical ventilation develop chronic crippling or even fatal lung disease as a result of the high ventilation pressures and high oxygen levels needed to keep them alive in the short term. Two Canadian and eight U.S. centers are testing whether HFV can provide adequate gas exchange in infants at low pressures and with lower oxygen levels than those needed with conventional ventilators.

China: An agreement between the Government of the United States and the Government of China on cooperation in Science and Technology was signed in January 1979. The subsequent U.S.-China Protocol for Cooperation in Science and Technology of Medicine and Public Health, signed in June 1979, identified cardiovascular disease as one of seven areas of cooperation. In 1984, cooperative activities were expanded to include cardiopulmonary disease. Cooperation with China provides unique opportunities for joint epidemiologic research employing standardized techniques. Both China and the United States exhibit geographic variations in the prevalence of

hypertension. In China, the prevalence is higher in the North than in the South. The converse is true for the United States. In China, as in other developing countries, an increase in urbanization appears to be associated with an increase in average blood pressure.

In 1981, a U.S.-China program was launched to study the epidemiology of cardiovascular and cardiopulmonary diseases according to a joint research protocol. It involves a population of more than 11,000 men and women, ages 35–54 years at entry to the study, from four population samples, including 3,290 steel workers and 2,850 farmers in Beijing (North China) and 2,510 shipyard workers and 2,850 farmers in Guangzhou (South China). Baseline surveys were carried out from 1981 to 1985 and included detailed medical history, blood pressure, body weight, height, pulmonary function, electrocardiography, and determination of serum lipids. Also, additional measurements were carried out on a 10 percent subsample of each population group. In the spring of 1986, the field work was completed for the prevalence phase (Phase I) of the study.

During the past 6 years, joint U.S.-China working meetings were held once or twice a year in either the United States or China. In July 1987, a five-member U.S. group visited Beijing to make final plans for the incidence phase (Phase II) of the study Phase II field work commenced in September 1987 and will involve followup and periodic rescreening of the population groups seen in Phase I as well as younger and older age groups. Risk factors targeted for intervention include smoking, hypertension, and lipid and salt intake.

Large segments of Phase I epidemiologic data from North and South China have been entered on microcomputers in Beijing, Guangzhou, and at the University of North Carolina Data Analysis Center. During the 1987 meeting in Beijing, the Chinese side provided study data from the Chinese populations that had been computerized since the 1986 U.S. visit. The U.S. side provided data from the Lipid Research Clinics (LRC) prevalence survey data (1972–78). A preliminary book of the Chinese data received during the 1986 data exchange was prepared at the North Carolina Data Analysis Center and provided to the Chinese side.

In January 1987, a biostatistician from South China commenced a year of training in biostatistics and epidemiology at the Data Coordinating Center and the University of North Carolina. An epidemiologist from Beijing also worked at the Data Analysis Center to assist in the computerization of joint data.

A U.S. pulmonary expert visited Beijing and Guangzhou in July 1987 to prepare for the fall 1987 field work and train Chinese pulmonary technicians. He also repaired and calibrated the spirometry equipment.

Preliminary analyses of the data collected in China during 1981–87 and comparisons of these data with data from U.S. populations have been carried out. These analyses show that:

- For both Chinese men and women, workers' and farmers' mean blood pressure, prevalence rate of hypertension, and body mass index were significantly lower in the South than in the North. Sodium excretion and the Na/K ratio were correspondingly lower in the southern subgroups;
- The mean serum total cholesterol for each of the four sex-occupation groups was lower in the South than in the North. Also, farmers had lower levels than workers;
- The cholesterol levels of all Chinese populations were significantly lower than the levels found in the U.S. LRC populations; and
- The serum HDL-cholesterol levels were higher for Chinese men than U.S. men.

Other U.S.-China cooperative activities took place in FY 1987 that were not directly related to the U.S.-China Agreement. In October 1986, the Director, Beijing Heart, Lung, Blood Vessel Medical Center (BHLBC) and Anzhen Hospital, Beijing, visited NHLBI for discussions with the Institute's Associate Director for International Programs. In FY 1986, BHLBC sponsored an international symposium on cardiothoracic surgery in which leading U.S. surgeons from Harvard, NHLBI, Pittsburgh, Denver, and San Diego participated. BHLBC's community programs reach 100,000 to 150,000 people; it collaborates with 18 centers throughout China and is responsible for coordination of China's WHO MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project. The Chinese MONICA component includes approximately 700,000 persons. NHLBI also cooperates with WHO on the MONICA project. A BHLBC epidemiologist is currently receiving advanced training in the NHLBI Division of Epidemiology and Clinical Applications as a WHO Fellow.

In September 1987, the Devices and Technology Branch, NHLBI, briefed a delegation from the National Institute for Control of Pharmaceutical and Biological Products, Ministry of Public Health, China, on the status of the U.S. Artificial Heart Program, the Cardiac Assist Program, and the Biocompatible

Materials Program. Testing of hemocompatibility of biomaterials was a major theme of the discussions.

To gain an appreciation of the diversified geographic, social, and economic environments within which WHO Fellows are receiving their training in the United States, five members of the International Health Fellowship Committee, Chinese Ministry of Public Health, met with senior NHLBI staff in September 1987.

Czechoslovakia: The Associate Director for International Programs, NHLBI, visited Czechoslovakia in March 1987 on behalf of the Director, NHLBI, to explore the potential for scientific cooperation. Scientists from Czechoslovakia have long been active in international research and cooperated indirectly with NHLBI through the World Health Organization. Scientists and administrators of the Czech Socialist Republic, Prague, and the Slovak Socialist Republic, Bratislava, have developed a number of preproposals outlining specific scientific opportunities of potential mutual interest and benefit.

France: Joint studies are conducted under the agency agreement between the NIH and the Institut National de la Santé et la Recherche Médicale (INSERM).

During FY 1987, a French scientist visited the United States to continue joint studies with NHLBI intramural researchers on interstitial lung diseases. The research focuses on the study of mesothelial cell populations of the alveolar wall in normal humans and in patients with idiopathic pulmonary fibrosis, which is the prototype disease of interstitial fibrotic disorders. During the visit, the cell descriptions, cell counts, and statistical evaluations were completed and a joint manuscript was prepared for publication.

Two French scientists visited the United States to initiate joint research in pulmonary medicine and biology. The program focuses on the regulation of lysozyme expression in tracheal serous cells. One of the French scientists has detected large amounts of lysozyme in the culture medium of a serous cell line. The U.S. and French scientists tested the hypothesis that absence of lysozyme in certain media reflects a defect of gene transcription. Experiments were conducted to identify the factors that either inhibit gene expression in "lysozyme-restrictive" cultures or those that promote gene expression in the "permissive" cultures.

Joint research with France includes studies of the pulmonary aspects of HIV infection. This cooperation is part of a multinational effort by NHLBI to collect information on pulmonary complications caused by HIV infections in individuals in various risk groups and determine the pulmonary disorders in recently diagnosed patients with AIDS, in recently diagnosed patients with AIDS-related complex, and in individuals asymptomatically infected with AIDS.

Federal Republic of Germany: The United States and the Federal Republic of Germany are cooperating in biomedical research under an agreement signed in 1976. NHLBI cooperates in cardiovascular research, pulmonary research, and the pulmonary complications of AIDS.

Since 1980, U.S. and German investigators have collaborated on the design, planning, and execution of the German Cardiovascular Prevention Study (GCP) and the German National Health Survey (NHS) to make these studies comparable with those in the United States. The NHS is complete and the intervention phase of the GCP is in its third year at five sites. The goal of the GCP is to reduce cardiovascular mortality by 8 percent over an 8-year period.

One of the GCP intervention communities is located in Bremen. The 1984 baseline survey showed prevalence rates of hypertension of 20.2 percent in males and 23.2 percent in females in the age group 25–69 years. A comprehensive antihypertension program was organized in 1986 using methods modeled on the U.S. National High Blood Pressure Education Program. Extensive campaigns were carried out through print and electronic media to increase public awareness, and free blood pressure screenings were made available. Low-salt, low-cholesterol foods also were made available in cafeterias, restaurants, and bakeries. The antihypertension campaign was repeated in 1987. Other GCP centers are using the Bremen experience as a model.

Cooperation continues in the area of detection, prevention, and treatment of hypertension. A German National High Blood Pressure Program (GNHBP), modeled on the U.S. National High Blood Pressure Education Program, has been launched. The Director, NHLBI, is a member of the GNHBP Coordinating Committee. A National High Blood Pressure Conference and consensus meetings have been held. Also, a German High Blood Pressure Newsletter is being circulated to more than 50,000 physicians, and liaison has been established with the insurance industry and the worksetting. A U.S.-FRG workshop on blood pressure education and control was held in conjunction with the U.S. national conference on high blood pressure control in April 1987.

German and U.S. experts met in Heidelberg in February 1984 to initiate cooperative activities on basic and clinical research in pulmonary fibrosis. A U.S.-

FRG joint workshop was held in Heidelberg later in 1984. During FY 1985 and FY 1986, attempts were made to link ongoing pulmonary research in the United States and the FRG. A joint proposal was made to cooperate on basic, clinical, and epidemiologic research on the impact on the respiratory system of exposure to particles, fibers, and chemicals.

A planning meeting was held in Bonn in March 1987 for two joint U.S.-FRG workshops organized by the pulmonary research group at the Harvard School of Public Health and a research group in Frankfurt.

In February 1987, the director of the Pneumology Department at the Albert-Ludwigs-University, Freiburg, visited the Pulmonary Center, Boston University School of Medicine, to exchange research methodologies and identify topics for cooperative research. The German group is studying aerosol deposition in humans. Alveolar deposition is obtained using bronchoalveolar lavage, and bronchial deposition is measured directly in patients who are undergoing pulmonary surgery. The German scientists are treating children with cystic fibrosis with aerosols containing antibiotics and diuretics. They also are investigating markers of lymphocyte and macrophage activation.

The director of the Harvard research group made a reciprocal visit to institutes in Frankfurt and Munich. The first workshop, entitled "The Work Environment: Where Do Inhaled Aerosols Deposit? How Can Surrogate Aerosols Be Used To Diagnose Occupational Lung Disease?", will be held in Boston in October 1987, the second will be held in the Federal Republic of Germany in May 1988. In September 1987, a scientist from Munich commenced 3 months of joint research at Harvard on structural changes of the respiratory tract during chronic exposure to pollutants, in followup of earlier joint work.

A U.S. scientist visited laboratories in Frankfurt, Bochum, and Munich in January and October 1986. He presented a seminar entitled "Altered Collagen Crosslinking in Pulmonary Fibrosis, An Experimental, Clinical, and Structural Approach" and initiated collaboration with the Institute of Pathology, University of Munich. This Munich group has access to large numbers of lung biopsies. Samples are available from patients with adult respiratory distress syndrome and idiopathic pulmonary fibrosis as well as age-matched controls. The Munich group will characterize the lungs pathologically and clinically, and the U.S. group will perform correlative studies on the biopsies of collagen structure and cross-linking. Researchers at the Coal Miners Institute for Silico-Tuberculosis Research in Munich are interested in correlating their detailed, long-term clinical records of patient populations with evaluations of the collagen structure in silicotic lungs, using autopsy material. In April 1987, the director of this institute, together with several board members, visited U.S. Pulmonary Specialized Centers of Research (SCOR) and NHLBI to observe U.S. approaches to linking basic research and clinical practice.

The head of the Institute of Immunology, Marburg, visited the Pulmonary SCOR program at the University of Vermont in September 1987. A joint research project was developed. The Vermont group will expose rats to an aerosol of silica dust to produce a controlled degree of silicosis, and the Marburg group, using immunologic assays, will determine specific aspects of macrophage activation and lymphocyte-macrophage interactions.

The FRG Ministry of Research and Technology has agreed to participate with NHLBI in a longitudinal multicenter study on the pulmonary complications of HIV infection. The trial will assess pulmonary disorders in recently diagnosed patients with AIDS and with AIDS-related complex and in individuals asymptomatically infected with HIV.

During FY 1987, cooperative activities in blood resources continued to focus on exchanges of information on blood safety and the outbreak of AIDS in the United States, FRG, and Europe.

Greece: U.S. and Greek scientists share an interest in research on thalassemia and approaches to therapy through molecular biology. In March 1986, an agreement was signed between the NIH and the Institute of Molecular Biology and Biotechnology (IMBB) in Crete to begin collaborative activities in biomedical research including areas related to NHLBI.

Hungary: A bilateral agreement between the United States and Hungary for cooperation in the health sciences was signed in 1979. U.S. scientists provided sophisticated diagnostic procedures; the Hungarian side has provided access to a large patient population that suffers from valvular heart disorders. Scientist exchanges continued, with emphasis on innovation in diagnostic techniques for coronary and congenital heart disease.

Computer-assisted cineangiography has been explored as a means to assess ventricular wall dysfunction during acute myocardial infarction. As a result of progress in joint research employing this technology, a satellite computer link was installed during FY 1987 between the Hungarian Institute of Cardiology (HIC) and the University of Washington, providing an exchange of angiographic data and the results of analyses.

Collaboration continued among the University of California, Irvine, Long Beach Veterans Administration Medical Center, and HIC. Projects included a prospective evaluation of the use of computerized analysis of exercise electrocardiograms in diagnosing coronary artery disease, exploring the use of probabilistic methods to calculate the severity of coronary artery disease risk in patients with chest pain syndromes. Research centered on improving the sensitivity of these evaluations using computers in order to help assess the need for coronary angiography, percutaneous transluminal coronary angioplasty, or coronary artery bypass surgery.

Joint research continued on the clinical application of continuous-wave Doppler echocardiography to measure intracardiac blood flow velocities and determine gradient, pressure, and flow. This noninvasive method makes it possible to study many of the cardiac hemodynamic parameters that previously could be measured only through invasive catheterization.

A scientist from HIC collaborated with researchers at Vanderbilt University in studies of arrhythmias during postoperative care for open-heart surgery and acute renal failure in infants following open-heart surgery.

The U.S.-Hungary agreement has been extended in scope to include pulmonary disease research, with emphasis on the causes and contrasting trends of chronic obstructive pulmonary disease.

India: Collaborative projects between U.S. and Indian researchers are supported by the U.S.-India Fund for Cultural, Educational, and Scientific Cooperation. At the invitation of the Indian Minister of Health and Family Welfare, the U.S. Secretary of Health visited India in April 1987. The progress of the ongoing U.S.-India health research was discussed, and respiratory diseases were designated as an important area of collaboration.

The Division of Lung Diseases, NHLBI, continued to explore collaborative projects in high altitude research and chronic obstructive lung diseases. Both of these areas were discussed during a visit to India by the Director of the Division of Lung Diseases and a U.S. pulmonary specialist.

U.S. and Indian investigators are developing a collaborative project to explore neuronal and brain tumor-specific antigens using monoclonal antibodies in efforts to better characterize neuronal growth patterns in health and disease.

Israel: U.S. cooperation with Israel in health research was initiated in 1980 through an agreement signed between the two governments. Areas of potential research have been identified through discussions in Israel between the Associate Director for International Programs, NHLBI, and senior officials of the Israeli Ministry of Health. The U.S. remains interested in joint studies of sex differences in arteriosclerosis, molecular mechanisms of heart and vascular diseases, identification of cells in atherosclerotic plaques, and aspects of inflammatory processes in atherogenesis. Research has been proposed on lung structure and function of cholinergic receptors in circulating lymphocytes and alveolar macrophages. Israel also has proposed joint research on thalassemia. U.S. and Israeli scientists have proposed joint research on cardiovascular reactivity patterns under stress in order to study the role of biobehavioral factors in the development of hypertension.

Italy: U.S. cooperation with Italy was initiated in 1978 through a Memorandum of Understanding signed by the Secretary, Department of Health, Education, and Welfare and the Italian Minister of Health. NHLBI cooperation focuses on joint cardiovascular and pulmonary research. A series of joint symposia have been held, and the proceedings of seven of these have been published. A joint symposium entitled "State of the Art on Cholesterol and Triglycerides as Risk Factors for Cardiovascular Disease" was held in Florence in October 1986. The symposium included basic, clinical, and epidemiologic findings on cholesterol and related lipids. The next U.S.-Italy symposium in the cardiovascular area will be held in the United States in 1988 on magnetic resonance imaging in cardiovascular diseases. The next symposium in the pulmonary area will be held in the United States on the usefulness and perspectives of bronchoalveolar lavage with special emphasis on situations of bronchial inflammation and interstitial lung disease.

Correlations between elevated cholesterol levels and the development of atherosclerosis have been documented, and efforts continue to define more closely the genetic and environmental determinants of lipid and lipoprotein levels.

The Director, NHLBI, visited Italy in April 1987 to co-chair a meeting on biotechnology in cardiovascular diseases during the International Symposium on Biotechnology in Clinical Medicine. In July 1987, the Director served as an international advisory board member at the International Symposium on Cholesterol Control and Cardiovascular Diseases—Prevention and Therapy, held in Italy.

U.S.-Italy scientist exchanges in FY 1987 addressed studies to characterize and improve the pharmacologic properties of a lactosaminated FAB fragment,

a reagent that selectively induces catabolism of low-density lipoprotein (LDL) by the liver. (FAB refers to the fragment of immunoglobulin chain that carries the antigen binding site.) This has possible clinical applications for patients resistant to currently available pharmacologic therapies. In addition, GISSI, the Italian group for the study of streptokinase in myocardial infarction, and the U.S. Thrombolysis in Acute Myocardial Infarction (TIMI) study group are assessing thrombolytic treatment to reopen occluded coronary vessels. Results from TIMI Phase I established that tissue-type plasminogen activator holds more promise as an intravenous thrombolytic agent in acute myocardial infarction than does streptokinase.

In the pulmonary area, a scientist from the University of Padua, Italy, worked with researchers at the University of California Medical Center, San Francisco, on studies to determine whether late asthmatic reactions and the associated increase in airway responsiveness induced by toluene diisocyanate in sensitized subjects are associated with changes in inflammatory cells in the bronchoalveolar lavage.

A U.S.-Italy meeting on hyperreactivity of the airways was held in San Francisco in September 1986. Topics included effects of chronic inflammation on airway responsiveness, cardiovascular effects of histamine and sulfidopeptide-leukotrienes, and possible interaction of purinergic and prostanoid systems in the modulation of tracheal tone and airway reactivity. In February 1987, a meeting was held in Washington, D.C., on asthma self-management, to review data from the collaborative research project on this topic and to plan followup. Clinics have been set up in Italy to replicate NHLBI programs to promote effective management of asthma by asthmatic children and their families. A scientist from the Mario Negri Institute of Milan visited colleagues at the Johns Hopkins University in Baltimore for joint research on purinergic receptors on human pulmonary mast cells and macrophages.

Japan: Cooperative research with Japan is conducted under the Agreement for U.S. and Japan Cooperation in Research and Development in Science and Technology, signed in May 1980 and extended to October 30, 1987.

The United States and Japan share a high prevalence of hypertension, yet its outcome differs significantly between the two nations. In Japan, stroke is the more common outcome of hypertension, whereas in the United States, heart attack is more usual. Cooperative research in FY 1987 continued in four areas:

- Prevention of hypertension through nonpharmacologic approaches;
- Blood pressure and other cardiovascular risk factors among children and young adults;
- Pathology of arteriosclerosis and hypertensive vascular lesions; and
- Community intervention and prevention of cardiovascular disease.

The spontaneously hypertensive rat (SHR) has been used worldwide as a model for the study of pathogenesis of hypertension and its complications, including myocardial involvement and stroke. These genetic models, predisposed to hypertension and stroke, have been used in studying the protective influences of a low-salt, high-protein diet in guarding against stroke. In FY 1987, a scientist from the Honolulu Heart Program visited Japan to compare pulmonary function to cardiovascular disease risk. Despite the close associations between heart and lung function, few studies have documented the relationship between impaired pulmonary function and cardiovascular disease risk. The study will help broaden understanding of the influences and interactions of risk factors that predispose individuals to heart disease.

U.S. and Japanese investigators are conducting epidemiology studies to measure blood pressure levels and cardiovascular risk factors in children and young adults. It is only within the last decade that researchers have begun to examine the early natural history of hypertension. As a result, understanding of the pathogenesis of this condition is changing.

U.S. and Japanese researchers are also exploring cardiovascular risk factors through pathoepidemiologic studies. Atherosclerosis is being measured in pathological specimens collected and analyzed in both countries using standardized techniques. The prevalence of atherosclerotic lesions in the coronary artery and abdominal aorta of a population studied in the United States was three times higher than in the Japanese cohort.

The Japanese have conducted a 23-year morbidity study of coronary heart disease (CHD) and stroke in urban and rural populations in northeast prefectures of Japan. The University of Tsukuba and the University of Minnesota have collaborated to analyze the extensive data base from this study. A dramatic decline of stroke incidence was observed in men and women of every age group from under 70 years. This favorable trend is attributed to downward shifts of mean values and distribution of blood pressures over the past two decades, largely as a result of decreased sodium consumption. In addition, increased intake of meats and dairy products is thought to have lessened risk of stroke by increasing protein intake, a

nutrient that is theorized to generate biochemical mechanisms in the body that protect against stroke. Epidemiologists and public health officials in Japan are becoming more attentive to lipid and lipoprotein levels to ensure that increased availability of meat products will not dramatically raise cholesterol levels and unfavorably alter the incidence of CHD.

Korea: Cooperation between the United States and Korea is being carried out under the U.S.-Korea Science and Technology Agreement signed in 1976 and renewed in 1986. A Korean Advanced Institute of Science and Technology—U.S. Joint Symposium on Life Science was held in Seoul, Korea, in October 1986. During the past 10 years, NHLBI intramural laboratories have had extensive exchanges with Korean scientists. Cooperation with Korea includes the application of recombinant DNA technology, monoclonal antibody techniques, and other technical advances in molecular and cellular biology. Advances in genetic engineering have implications for the diagnosis and treatment of a number of disease problems addressed by NHLBI, such as genetically based diagnosis of inherited diseases.

Mexico: In January 1986, U.S. officials visited Mexico to explore biomedical research opportunities of mutual benefit. Under the auspices of the NIH bilateral agreement with Mexico, signed in 1985, NHLBI has agreed to consider cooperation in hypertension as well as other areas.

Nigeria: U.S. and Nigerian scientists are proposing to cooperate on studies of respiratory distress syndrome (RDS) in infants. In the United States, lung diseases account for 48 percent of all deaths of infants under 1 year of age, and RDS is one of the leading causes of infant mortality. U.S. scientists have found a lower incidence of RDS in black than in white babies. Nigerian scientists have isolated a special protein in the lungs of black babies that appears to be a protective mechanism against RDS. It is anticipated that cooperation in this area may lead to new information on the etiology of RDS in infants and possibly to better therapy for this usually fatal disease. A U.S. team will visit Nigeria in October 1987 to initiate plans for the joint studies.

Pakistan: In August 1987, the Executive Director of Pakistan's National Institute of Cardiovascular Diseases visited the NIH and NHLBI to discuss the potential for U.S.-Pakistan cooperation in the cardiovascular area. The National Institute of Cardiovascular Diseases in Karachi is interested in joint research in hypertension and coronary heart disease. Further details of the cooperation will be developed during a planned visit to Pakistan by the Director, NHLBI.

Poland: Cooperative research with Poland is conducted under the U.S.-Poland Agreement for Health Cooperation, signed in 1974, and the most recent U.S.-Poland collaborative research agreement, signed in 1984. NHLBI collaboration with Poland was initiated in 1978, and joint meetings have been held biennially to review progress and plan future projects.

Joint research with Poland offers special opportunities for U.S. scientists, given the contrasting risk of cardiovascular disease in the two nations. Although the incidence of coronary heart disease is high in both countries, mortality rates for men have declined by 35 percent in the United States between 1970 and 1982, whereas they have risen in Poland by 60 percent. Exploration of these contrasting trends may help to define risk factors and improve understanding of cardiovascular disease etiology.

Cooperation with Poland has included basic research, clinical studies, and epidemiologic studies. Examples are clinical studies of cardiomyopathies and the role of prostaglandin/prostacyclin metabolism in atherosclerosis. Joint epidemiologic studies are under way in Warsaw and Cracow to assess the prevalence of cardiovascular disease and risk factors within urban and rural settings. A proposed expansion of this study would include new blood lipid, pulmonary function, and hemostatic measurements to allow comparisons between Polish data and data from the largest U.S. prospective cardiovascular disease study, the Atherosclerosis Risk in Communities Study. Comparable data will assist researchers in identifying the risk factors responsible for mortality, broaden insights into disease etiology, and help to identify persons who are susceptible to heart disease. These studies are an outgrowth of the Polish participation in the WHO Trial of Multifactorial Prevention of Coronary Heart Disease, which was developed in the 1970s to assess the efficacy of primary prevention programs among European communities. A pilot study to test the feasibility of a full-scale U.S.-Poland trial was completed in 1981 as a component of the WHO European trial. U.S. data derived from the Lipid Research Clinic findings in Seattle, Washington, and Stanford, California, were compared to pilot study data from Poland. The Polish population had higher blood levels of triglycerides and high-density lipoprotein cholesterol (HDL), higher ratios of HDL cholesterol to total cholesterol, and higher prevalence of hypertension and smoking. Total cholesterol levels were lower in the Polish cohort.

The full-scale trial has now been completed. Cracow, Warsaw, and the United States each screened a total

of more than 2,600 men and women ages 35–64. The Polish data tape has undergone preliminary analysis at the Central Patient Registry of the LRC in Chapel Hill, North Carolina, and joint publications are being developed.

This study, which is incorporated within the WHO MONICA trial, not only expands the data base of the study but provides data comparable to those from the U.S. Lipid Research Clinic and Cohort Community Surveillance Programs. NHLBI provides computer processing and biostatistical analysis for this study through the Central Patient Registry of the Chapel Hill LRC. Laboratory standardization is supported through the Centers for Disease Control in Atlanta, Georgia.

A U.S.-Poland symposium on the etiology, pathogenesis, and treatment of coronary artery disease was held in Bethesda, Maryland, in September 1986. Scientists on both sides expressed continued interest in promoting scientific communication and joint research in areas of mutual interest.

U.S.-Poland activities in lung disorders focus on epidemiologic studies of chronic obstructive pulmonary diseases (COPD). The degree of impaired ventilatory function is a critical element in the natural history of COPD. Prospective studies have defined factors that impair ventilatory function and affect the incidence of COPD with age, and the detrimental influence of cigarette smoking has been well documented. Polish investigators have undertaken a study entitled "The Cracow Prospective Study of COPD," which assesses the influence of a wide range of risk factors on ventilatory function and COPD, including cigarette smoking and air pollution. A COPD longitudinal study employing a similar protocol was completed in Tucson, Arizona, and the results are being compared to the Polish data with emphasis on spirometry results related to cigarette smoking and disease symptoms.

Spain: The 5-year Treaty of Friendship and Cooperation, signed in January 1976 and renewed in 1982, and the U.S.-Spain Science and Technology Agreement signed in 1977 provide the framework for NHLBI administrative support for cooperation between U.S. and Spanish scientists. Projects are under way in the heart, lung, and blood disease areas.

The following projects are being implemented:

- Mechanisms Regulating Intracellular Protein Turnover;
- Respiratory Failure in Chronic Lung Diseases;
- Von Willebrand's Disease: Classification and Identification of Molecular Abnormalities;
- Thrombolysis in Acute Myocardial Infarction in Two Communities;
- Renal Function and Hypertension; and
- Metabolism of Lipoprotein, Triglyceride, and Cholesterol by the Placenta and Transport to the Fetus.

Thailand: NHLBI intramural and Thai scientists have proposed cooperation on aplastic anemia under the overall science and technology agreement signed in 1984. The relatively large number of aplastic anemia cases in Thailand provides scientists from both countries with an opportunity to test new hypotheses of causation and pathogenesis of this disease and to develop new approaches to treatment. NHLBI scientists plan to visit Thailand in 1988.

Turkey: The Deputy Minister of Health of Turkey, the Chairman of the Health Commission of the Turkish Parliament, and a Turkish university administrator visited NHLBI in April 1987. Interest was expressed in potential cooperation in the cardiovascular area, particularly in regard to studies of the genetic patterns of cardiovascular disease, for example, dyslipoproteinemias in various population groups in Turkey.

U.S.S.R.: The U.S.-U.S.S.R. Joint Committee for Cooperation in Public Health met in the United States for the first time in 8 years in April 1987. Progress in health cooperation for the 1978–86 period was reviewed, and plans for continued cooperation over the 1987–92 period were agreed upon. The U.S.-U.S.S.R. Agreement for Cooperation in Public Health was originally signed in 1972 for a 5-year period; the Agreement for Cooperation in Artificial Heart Research and Development was originally signed in 1974. Both agreements have been renewed periodically and were renewed again for the period 1987–92.

Since the original agreements were signed, cooperative activities in the cardiopulmonary area have grown to encompass eight programs of joint research (Areas 2 and 4 have been discontinued). The new agreement includes changes in the structure of the program. Some research areas have been renamed to reflect changes in scientific emphasis, and new areas have been added.

The results of cooperative activities in each of the eight areas during FY 1987 are summarized below. Nine U.S. scientists and one delegation (including 5 scientists) visited the Soviet Union for a total of 334 days, or 11 person-months; 17 Soviet scientists and three delegations (including 26 scientists) visited the United States for a total of 1,102 days, or 36.7 person-

months. Two joint symposia were held. The Fifth Joint U.S.-U.S.S.R. Symposium on Arterial Hypertension (Area 7) was held in March 1987 in Easton, Maryland. The Joint U.S.-U.S.S.R. Symposium on Heart and Lung Metabolism (Area 3) was held in Asheville, North Carolina, in September 1987.

Area 1: Pathogenesis of Arteriosclerosis. This area focuses on basic and clinical research to investigate lipoprotein atherosclerosis interactions. Joint studies relate directly to the basic research questions resulting from ongoing epidemiologic studies. Exchanges of scientists have been initiated for investigations of lipoprotein structural studies using magnetic resonance imaging and other structural probes and the molecular and cell biology of lipoproteins.

A Soviet scientist visited the Molecular Diseases Branch, NHLBI, to continue joint studies on the mechanisms of regulation of gene expression, including coding for lipoproteins by cholesterol and lipids. The objective of these joint studies is to define human apolipoprotein biosynthesis from the levels of transcription through posttranslational modifications.

The Second Joint U.S.-U.S.S.R. Lipoprotein Symposium, held in September 1986 at the NIH, included presentations on basic, clinical, and epidemiologic research. The proceedings will be published in English in 1988.

Epidemiology studies, including the U.S.-U.S.S.R. joint Lipid Research Clinics studies (which are an extension of the NHLBI-sponsored U.S. LRC program previously included in Area 1) have been moved to a new Area 8, Cardiovascular Epidemiology and Prevention. This was a result of a mutual decision at the U.S.-U.S.S.R. Joint Health Committee meeting in April 1987.

Area 2: Coronary Heart Disease. This area was discontinued in FY 1987.

Area 3: Cardiovascular Biology and Medicine. Joint activities in Area 3 have included exchanges of scientists in basic research on the biochemical, biophysical, and cellular aspects of heart and lung metabolism in health and disease. In April 1987, both sides agreed that expansion of research activities warranted the separation of pulmonary and cardiovascular activities with formation of a new area, Area 9, Pulmonary Biology and Medicine, and renaming of Area 3.

A Joint U.S.-U.S.S.R. Symposium on Heart and Lung Metabolism was held in Asheville, North Carolina, in September 1987 on the structure and injury of the heart and vascular wall and on signal transduction in heart and lung cells. Each side will publish the proceedings of the symposium in its own language. Joint research will continue in 10 areas:

- Calcium metabolism, contractile regulation, and the cytoskeleton;
- Hormones, prostaglandins, cyclic nucleotides, and protein phosphorylation;
- Protein metabolism and morphogenesis;
- Energy metabolism in the heart;
- Mechanisms of ischemic damage;
- Use of liposomes for delivery and targeting of drugs in the heart;
- Membrane structure and function;
- Endothelial cell physiology and pathophysiology;
- Connective tissue physiology and pathophysiology; and
- Smooth muscle physiology and pathophysiology.

At the symposium, both sides emphasized the need to continue to develop the research technology in the following areas:

- Structure-function relationships of proteins serving as receptors, ion channels, and other signaling proteins in heart and vascular cells using recombinant DNA technology, site-directed mutagenesis, and other techniques of molecular biology; and
- Control of expression of genes for receptors, ion channels, signaling proteins, and cytoskeletal and extracellular matrix proteins in the heart and vascular system.

A U.S. scientist visited the U.S.S.R. in May 1987 to continue joint studies on immunoliposome-based diagnostic procedures for cardiovascular diseases. This work also is directed toward the development of targeted delivery of therapeutic drugs and peptides to specific sites in the cardiovascular system.

A U.S. scientist visited the U.S.S.R. for 2 months starting in June 1987 to continue joint studies on purification of a vascular smooth muscle calcium channel. Purification of this calcium channel would permit structural and functional analyses that should enhance understanding of the regulation of intracellular calcium concentration in vascular smooth muscle and provide insights into the regulation of vascular tone.

A Soviet scientist worked at the Cardiovascular Research Institute in San Francisco on a joint physiologic study of cardiomyopathy in animal models. It was determined that before the stage of cardiac fail-

ure, there was increased diastolic stiffness of the left ventricle. A joint manuscript is in preparation. Another Soviet scientist continued joint experiments at Massachusetts General Hospital and at the University of Tennessee on drug targeting of liposomes.

Area 4: Congenital Heart Disease. This area was discontinued in FY 1987.

Area 5: Sudden Cardiac Death. Exchanges of scientists to carry out basic research on the pathological anatomy and electrophysiology that may lead to sudden cardiac death and on the pharmacology of possible prophylactic antiarrhythmic drugs continued to provide the focus for activities in Area 5 during FY 1987.

In October 1986, a U.S. scientist visited the U.S.S.R. to continue joint studies on the mechanism of action of the antidysrhythmic drug ethmozin in isolated heart cells. A joint manuscript will be submitted for publication.

Two Soviet scientists visited the United States in May–June 1987 to continue joint studies. One scientist worked at the University of Nebraska on isolated guinea pig ventricular muscle preparations to determine the electrophysiologic effects of high-energy phosphate compounds on the cardiac action potential during ischemia and the antiarrhythmic effects of the drug ethacizine on abnormal automaticity. This scientist also visited Duke University to study the effects of ethacizine on ionic currents and intracellular pH in cultured heart cells. The other scientist worked at the University of Alabama at Birmingham on the ultrastructure of the cardiac conduction system in the human heart. Specimens of sinus node and AV node early postmortem material were jointly examined.

Area 6: Blood Transfusion and Blood Resources. Two Soviet scientists visited the United States in November 1986. One scientist developed a joint project proposal on a "U.S.-U.S.S.R. Cooperative Prospective Study of Transfusion Transmitted Diseases in Patients With Congenital Coagulation Disorders." This would parallel the NHLBI-sponsored Transfusion Safety Study and give an added dimension to the data being collected in high- and low-risk U.S. cities. The proposal is under consideration for possible implementation.

Joint work by the other Soviet scientist was designed to continue research to improve methods of plasmapheresis. Manuscripts were prepared for publication.

Two Soviet scientists visited the United States in May 1987 to continue joint studies on the preservation of blood platelets. One scientist worked at the American Red Cross Blood Center comparing the properties of platelet storage bags from the Soviet Union with PL732 Fenwal bags used in the United States. The two kinds of storage bags were found to have similar gas transport properties. The second set of studies explored whether thrombin inhibitors could improve platelet storage.

The other Soviet scientist worked at the University of Minnesota on physiologic, biochemical, and morphologic studies of platelets collected and stored under different controlled conditions to determine whether platelet survival can be extended beyond current limits.

Area 7: Hypertension. U.S.-U.S.S.R. cooperation in Area 7 is designed to develop better methods of prevention and control of the potentially lethal sequelae of hypertension, a serious problem in both the United States and U.S.S.R. The collaboration includes basic science, biobehavioral research, and prevention of hypertension.

The Fifth Joint U.S.-U.S.S.R. Symposium on Arterial Hypertension was held in March 1987 in Easton, Maryland. The proceedings will be published in English in April 1988. Research will continue in the following areas:

- Basic research on the mechanisms involved in blood vessel constriction at the organ, cellular, and molecular levels;
- Clinical research on the pharmacology of antihypertensive drugs and the interactions between the cardiovascular and renal/adrenal hormone systems;
- Biobehavioral aspects of hypertension and associated therapeutic implications;
- Epidemiology and prevention of hypertension in children; and
- Strategies for improving nonpharmacologic and pharmacologic control of hypertension in individual patients and in population groups.

Five Soviet scientists visited the United States in November 1986 to continue joint studies on basic research on hypertension, biobehavioral treatment in U.S. and Soviet populations, essential hypertension in nonhuman primates, and primary prevention of hypertension in adolescents.

Exchanges with the University of Minnesota resulted in the replication of a U.S. pilot study in the U.S.S.R. in the epidemiology of essential hypertension in adolescents. One of the Soviet scientists conducted joint work on a comparison of the effective-

ness of treating hypertension using autogenic training developed in the Soviet Union with biofeedback methods developed in the United States. Preliminary analyses indicate that the U.S. and U.S.S.R. nondrug treatments are equally effective cross-culturally and that studies from either country should yield conclusions valid for either population. Continued joint research is proposed to focus on thermal biofeedback to improve understanding of the mechanisms by which this therapy exerts beneficial impact on hypertension.

Two Soviet specialists visited the Seattle Regional Primate Center to continue joint research on essential hypertension in primates. The scientists learned about the equipment and set-up that will be used in joint studies at the U.S.S.R. Primate Research Center in Sukhumi. Joint research was conducted in April–May 1987 on the special strain of baboons available in the U.S.S.R. The studies were designed to investigate the interrelationship of laboratory-defined stressful situations and cardiovascular functioning, either pathologic or normal. The pilot studies for this project were carried out as planned, and the data are being analyzed for publication.

Three Soviet scientists visited the United States in March 1987 to continue studies with U.S. scientists on basic research of hypertension. One scientist worked at the NHLBI intramural research program, Laboratory of Molecular Cardiology, and two worked at Vanderbilt University.

Area 8: Cardiovascular Epidemiology and Prevention. Activities in Area 8 derive from a series of epidemiologic studies that have been under way since 1972 under Area 1. At the joint U.S.-U.S.S.R. Health Committee meeting in April 1987, both sides agreed that the joint epidemiology studies conducted as an extension of the NHLBI-sponsored LRC program should be continued in Area 8 rather than Area 1. This decision derives from the success of the ongoing studies and the anticipated success of future project proposals in the epidemiology area.

Studies in Area 8 take a multidisciplinary and multiclinic approach to research on plasma lipids and lipoproteins as they relate to atherosclerotic disease. The U.S.-U.S.S.R. studies have included the participation of nine U.S. LRCs and two clinics supported by the U.S.S.R. Ministry of Health. The participating populations are representative of diverse ethnic, occupational, geographic, and age groups. This makes possible cross-cultural comparisons of the differences in risk factors between the Soviet and U.S. populations in order to enhance understanding of the overall disease process. In September 1986, the Second Joint U.S.-U.S.S.R. Lipoprotein Symposium was held at the NIH. The results of the LRC Prevalence Study and U.S.S.R. Second Prevalence Study and the Joint Mortality Followup Study were reported at the symposium; the proceedings will be published in *Atherosclerosis Reviews* in 1988.

A joint abstract entitled "High-Density Lipoprotein Cholesterol and Mortality in U.S.S.R. and U.S. Middle-Aged Men: The Collaborative U.S.-U.S.S.R. Mortality Followup Study" has been accepted by the American Heart Association for presentation at its annual meeting in November 1987. Other joint manuscripts are being prepared for publication.

Area 9: Pulmonary Biology and Medicine. Joint research in this newly formed area builds on activities previously conducted under Area 3. In conjunction with the U.S.-U.S.S.R. Symposium on Heart and Lung Metabolism in Asheville, North Carolina, in September 1987, plans were made for exchange activities in Area 9.

Exchanges of scientists will be continued and expanded in basic and clinical pulmonary research with emphasis on the use of technologies of molecular and cellular biology. Three areas will be emphasized:

- Lung cell biology including both vascular endothelial and airway epithelial cells;
- Biochemistry of lung cell receptors and transmembrane signaling; and
- Pulmonary hypertension and asthma.

Two U.S. scientists visited the U.S.S.R. in March 1987 for joint research on pulmonary metabolism. One scientist explored the availability of human lung tissue for various types of structural and cell biology research. He was particularly interested in isolating alveolar type 2 cells from human lungs, and plans for several joint projects were developed. The other U.S. scientist continued studies of the effects of platelet activating factor (PAF) on pulmonary endothelial cells. Analyses suggest that pulmonary endothelial cells are not only a source but also a target for PAF. Binding of PAF to endothelial cells triggers metabolic and morphologic responses. The mechanisms of signal transduction appear to involve mobilization of intracellular calcium, increased phosphoinositide turnover, and activation of protein kinase C.

Three U.S.S.R. scientists followed up these visits in September–October 1987. They continued joint research with their U.S. counterparts on various aspects of pulmonary cell biology and prepared a series of joint papers for publication.

Area 10: Artificial Heart Research and Development. Activities under the U.S.-U.S.S.R. Agreement for Co-

operation on Artificial Heart Research and Development are directed toward the development of better biomaterials for circulatory devices and the study of the blood/biomaterials interface *in vitro* and *in vivo* to achieve this objective.

The U.S.S.R. Chairman for cooperation on artificial heart research and development visited the United States in October 1986 and in May 1987 to meet with his U.S. counterpart and discuss plans for further joint research.

The Soviet specialist who is coordinating joint activities in the biomaterials area visited the United States in October 1986 to continue joint research. Work is progressing well, and manuscripts were prepared for joint publication. An article entitled "The Organization of Albumin on Polymer Surfaces" will be published in *Proteins at Interfaces*, an American Chemical Society publication.

The joint work in biomaterials is based on the hypothesis that the blood compatibility of polymer implants is governed for clinically significant periods by the fate of plasma proteins adsorbed on the surface of the polymer. Conformational alterations of the proteins that release active fragments into the blood stream or provide active sites on surface-retained protein initiate deleterious processes, specifically coagulation, platelet adhesion/aggregation, and (alternate pathway) complement activation. Methods are being implemented to alter these events favorably and improve the blood compatibility of circulatory devices.

Three Soviet biomaterials experts visited the University of Utah in Salt Lake City in June 1987 to carry out studies of protein adsorption and calcification of polymer materials. The scientists used a flow cell with an improved design developed by the Soviet side.

Venezuela: A Memorandum of Understanding in biomedical research was signed in 1980 by the Venezuela Ministry of Health and the U.S. Department of State. U.S. and Venezuelan program coordinators have communicated about collaboration, particularly with regard to Chagas' Disease, which affects the heart and may lead to cardiomyopathy and sudden death.

Yugoslavia: NHLBI provides administrative support for U.S.-Yugoslavia research funded through the Special Foreign Currency Program of the Fogarty International Center. The following proposals have been submitted for NHLBI review and approved for funding by the U.S.-Yugoslavia Joint Board:

- Antihypertensive Effects of Heparin;
- Interactions of Metal Ions With Bioligands; and
- Molecular Organization of Plasma Lipoproteins.

A fourth project on pulmonary function in relation to age and occupation has been under way since March 1987. The Yugoslav investigator, who is a specialist in occupational medicine, visited NHLBI in August 1987 to discuss the project. She is currently investigating a number of occupational hazards related to airborne particulates associated with respiratory diseases.

Taiwan: Discussions have been held between U.S. and Taiwanese officials in the cardiovascular area, and agreement has been reached to cooperate in hypertension and stroke research. The chairman of the Department of Medicine, National Taiwan University, Taipei, visited NHLBI in July 1987 to discuss proposed projects.

Activities With International and Multinational Organizations

During FY 1987, NHLBI continued cooperation with international agencies. The Institute is a WHO Regional Collaborative Center for Research and Training in Cardiovascular Diseases for the Americas. As a Collaborating Center, NHLBI carries out three major functions:

- Provides advisory services to WHO;
- Assists in the training of suitable, qualified WHO Fellows; and
- Assists and provides advice in the collection and exchange of information on activities in the field of cardiovascular disease research.

NHLBI collaborates directly with WHO Headquarters in Geneva, with the Pan American Health Organization (PAHO), and also with regional offices around the world. The designation of NHLBI as a WHO Collaborating Center has facilitated the Institute's cooperation with WHO in a wide range of international activities of mutual interest and concern. The Director, NHLBI, and senior Institute staff have participated in WHO advisory committee meetings and contributed to WHO reports in several areas, including the WHO Cardiovascular Diseases Steering Committee, the Intensified Program for Prevention of Cardiovascular Disease, the Community Control Programs, Hypertension, and the MONICA Project.

The Epidemiology and Biometry Program of the Division of Epidemiology and Clinical Application,

NHLBI, is hosting a WHO Fellow from China from June 1987 until April 1988. She is comparing data from the Chinese MONICA project and other Chinese studies with U.S. data from the Framingham and Honolulu Heart Studies.

During FY 1987, NHLBI continued to provide contract support to the WHO MONICA project. This contract ensures that NHLBI will receive up-to-date data on the WHO MONICA project and fosters collaboration between MONICA and NHLBI's Study of Atherosclerosis Risk in Communities. NHLBI supports the MONICA project to ensure comparability of the data obtained by the two studies through standardization of procedures for coding classification and analysis of coronary and stroke events, risk factors, and medical care.

Extramural Programs

NHLBI is engaged in a broad range of research with foreign institutions through international grants, contracts, and fellowships. These activities provide important benefits to national research efforts and have drawn upon expertise and resources worldwide.

During FY 1987, NHLBI supported 27 foreign grantees working in Australia, Canada, China, Federal Republic of Germany, Israel, Italy, Romania, Sweden, Thailand, and United Kingdom.

Israeli scientists have developed a unique method to study the pathogenesis and regression of atherosclerosis. Romanian investigators are studying the biochemical factors and mechanisms in the prelesion stage of atherosclerosis and thrombosis.

Studies in Canada are assessing vascular flow patterns to correlate findings with the incidence of vascular disease. Other NHLBI international grants include:

- Basic studies on muscle ultrastructure in trachea, bronchi, and lung vessels;
- Blood cell deformability and adhesion experiments in Canada;
- Gene regulation in hypertension conducted in the Federal Republic of Germany; and
- Research by Canadian scientists on the mode of action and fate of heparin and its role in the development of circulatory devices.

Swedish pulmonary scientists are studying the biochemical properties of leukotriene C synthetase and its possible role in airway disease. In Australia, researchers are exploring the inhomogeneous properties of gas mixing and ventilation distribution in the normal state and among patients with various types of airflow obstruction. A second Australian grant is supporting use of new methods to study how the respiratory system copes with changes in its mechanical properties.

Two Canadian grants are supporting investigation of muscle dynamics in relation to respiratory disorders. Another Canadian group is studying the nature and sequence of toxic events following oxidative stress to investigate lung damage related to hyperoxic and drug therapy.

International grants in blood diseases include molecular research conducted by a Nobel laureate in the United Kingdom on conformational changes and adaptations of hemoglobin in sickle cell disease. In China, abnormal hemoglobins and various types of alpha- and beta-thalassemia are being examined through population studies. Canadian researchers are studying the pathogenic mechanisms that induce production of factor VIII inhibitory antibodies in a dog model of hemophilia.

NHLBI supports both U.S. and international components of standardized multicenter clinical trials under the contract mechanism. Twelve centers located in Belgium, Canada, and Sweden are participating in the following trials:

- Lipid Research Clinics Followup Studies;
- Studies of Left Ventricular Dysfunction (SOLVD) and the SOLVD Registry;
- Cardiac Arrhythmia Suppression Trial;
- High-Frequency Ventilation Intervention in Premature Infants; and
- Early Intervention for Chronic Obstructive Pulmonary Disease in Cigarette Smokers

NHLBI also supports the WHO MONICA study with a grant to its coordinating center in Helsinki, Finland.

Eight U.S. scientists are conducting research under NHLBI fellowships at universities in Australia, Sweden, and United Kingdom. Research topics address:

- Central serotonergic control of blood pressure;
- Afferent and efferent resetting of blood pressure levels in chronic hypertension;
- Central regulation of cardiovascular tone;
- The role of nerve cell physiology in blood pressure control;
- Complement-mediated cell adhesion to arterial walls;
- Cation binding sites in single capillaries;

- Ionic mechanisms of normal and abnormal cardiac rhythm; and
- The calcium current and sodium/potassium exchange in cardiac cells.

International Conferences, Seminars, and Meetings

NHLBI sponsored a number of conferences during FY 1987 involving international specialists in heart, lung, and blood diseases and blood resources.

In March 1987, NHLBI, the National Medical Association, and the Association of Black Cardiologists sponsored the Second International Interdisciplinary Conference on Hypertension in Blacks. The 3-day conference was co-sponsored by 152 groups including:

- The Cardiac Society of Uganda;
- The University of Ibadan, Nigeria;
- The University of the West Indies;
- The University of Dar es Salaam, Tanzania;
- The Kenya Medical Research Institute;
- Makerete Medical School, Uganda;
- The Medical School of Kinshasa, Zaire;
- Orstom Office de Recherche Scientifique, Senegal;
- The University of Zimbabwe; and
- The World Hypertension League.

The purpose of the conference was to seek to close the gap in the death rate and in morbidity from cardiovascular disease between blacks and whites through basic, clinical, and community research and education.

The Division of Lung Diseases, NHLBI, sponsored a 3-day international conference on primary pulmonary hypertension in May 1987 in which specialists from Japan, Europe, and Third World countries participated. The conference promoted scientific exchange at an international level and provided investigators access to populations about which they were relatively uninformed.

NHLBI also co-sponsored the Third International Conference on Acquired Immunodeficiency Syndrome held in June 1987. This conference reviewed all aspects of AIDS research.

Intramural Programs and Activities

Joint research was carried out in laboratories of the Division of Intramural Research, NHLBI, by 97 Visiting Scientists, 35 Guest Researchers, 2 exchange scientists, 2 research Fellows, a Fogarty scholar, and 9 volunteers. Countries and areas of origin include: Argentina, Australia, Austria, Bolivia, Brazil, Canada, China, Costa Rica, Egypt, France, Federal Republic of Germany, Greece, Iceland, India, Israel, Italy, Japan, Korea, Mexico, Nigeria, Poland, South Africa, Spain, Sweden, United Arab Emirates, United Kingdom, and Taiwan

During FY 1987, foreign researchers worked in each of the 17 branches of the NHLBI Division of Intramural Research. Foreign visitors to the Institute's laboratories were able to participate in more than 40 research projects using the most advanced techniques and instrumentation currently employed in cell biology.

Chapter VII
National Institute of Allergy and Infectious Diseases

Introduction

The National Institute of Allergy and Infectious Diseases (NIAID) was established by law in 1948 as the National Microbiological Institute. Its name change in 1955 reflected the increasing importance of disorders of the immune system as well as infectious diseases. NIAID assumed primary responsibility for NIH research in tropical medicine in 1968. In 1979, the Office of Recombinant DNA Activities, which monitors all Federally sponsored projects using this technology, was assigned to NIAID. In 1985, NIAID established the extramural Acquired Immunodeficiency Syndrome (AIDS) Program, and the NIAID Director is currently the NIH AIDS Coordinator.

Infectious and allergic diseases continue to be the most frequent reasons that patients seek medical attention in industrialized countries such as the United States. Globally, infectious diseases remain the major causes of morbidity and premature death. During FY 1987, the World Health Organization (WHO) established a Special Program on AIDS, and the U.S. Agency for International Development (AID) initiated two major cooperative agreements on AIDS Communication and AIDS Technical Assistance as international responses to the AIDS pandemic. New knowledge and research advances in the NIAID domestic research program are therefore extremely relevant to health authorities throughout the world and to international agencies with responsibilities for the application of research findings to disease prevention and control or clinical practice.

During FY 1987, NIAID initiated the International Collaboration in AIDS Research (ICAR) Program, designed to support U.S.-based research institutions in collaborative studies with foreign counterparts outside the United States. In recognition of the recent increase in tuberculosis in the United States, NIAID and the Centers for Disease Control (CDC) agreed in FY 1987 to work together to expand the national research effort in *Mycobacteria tuberculosis* and in atypical mycobacteria, which are opportunistic pathogens in immunosuppressed patients.

NIAID continues to assign high priority to filariasis, leishmaniasis, leprosy, malaria, schistosomiasis, and trypanosomiasis, the six disease complexes targeted by the United Nations Development Program (UNDP)/World Bank/WHO Special Program for Research and Training in Tropical Diseases (TDR). The NIAID Tropical Medicine activities, however, include other infectious diseases that are not endemic to the United States or occur at low levels but pose a threat to the health and safety of U.S. populations through importation, foreign travel, or residence overseas. These NIAID research areas include general parasitology; tropical bacteriology, mycology, and virology; rickettsioses; and vector pathogens. Examples of such diseases are amebiasis, giardiasis, trichinosis, cryptosporidiosis, cholera, syphilis, plague, rabies, and dengue fever viruses.

Highlights of Recent Scientific Advances Resulting From International Activities

Acquired Immunodeficiency Syndrome

In January 1987, the Epidemiology Branch of the AIDS Program announced interest in receiving program project grant applications for the Program for International Collaboration on AIDS Research. The ICAR Program is open to U.S. research institutions and is designed to encourage multidisciplinary collaborative research with foreign institutions. The joint research must be undertaken in a truly collaborative fashion, and at least 70 percent must take place outside the United States The research areas are broad and flexible. No restrictions are placed on the geographic location of the foreign collaborator. By the September 15 deadline, 15 applications involving research in Africa, Latin America, Southeast Asia, the Western Pacific, and Western Europe had been re-

ceived. The ICAR applications will undergo peer review in January 1988, and up to 10 awards may be made by midyear.

NIAID and the Pan American Health Organization (PAHO), which is also the Regional WHO Office for the Americas, entered into a 5-year research contract in June 1987 entitled "Studies of Human Immunodeficiency Virus (HIV) and Related Retrovirus Infections in Latin America and the Caribbean." PAHO/WHO and NIAID staff met with interested scientists from the Americas in Quito, Ecuador, in September 1987 to explain the scope of work and to generate proposals for projects outside the United States. Preliminary studies in high-risk groups in five or more countries will commence by early 1988. The preliminary studies will serve as the basis for longitudinal cohort studies on the transmission and natural history of HIV and other retroviral infections in the Region.

Elsewhere in the Caribbean, NIAID-supported investigators from the Cornell Medical College entered into the third year of a 5-year project to document the natural history of HIV infection in Haiti. During FY 1987, HIV seroprevalence in Haiti in adults ranged from 3 percent in rural areas to 37 percent in urban tuberculosis patients. Of Haitians meeting the PAHO/WHO diagnostic criteria for AIDS, 85 percent were seropositive; 55 percent of spouses or sexual partners and 18 percent of siblings and close friends were found to be HIV-seropositive. Cornell and Haitian investigators have described the transmission of HIV infection from patients with AIDS to their sexual partners and infants. The project is currently studying the natural history of HIV infection in this "second" generation of infected individuals. To date, the natural history of HIV infection among seropositive sexual partners has been progression to clinical AIDS at a rate of 1 percent per month—more than double the rates observed in prospective studies carried out in the United States. Diarrhea, wasting, and "malignant AIDS pruritus," an intense itchy skin condition, are much more common in Haiti than in the United States. By contrast, the prevalence of Kaposi's sarcoma is lower than in the United States and is decreasing.

During FY 1987, NIAID made a new award to the Johns Hopkins University and colleagues in Haiti to support HIV and HTLV-I cohort studies of Haitian women and infants. The cohort studies will enroll 3,000 pregnant women in the Port-au-Prince metropolitan area. The project will emphasize the effect of HIV and/or HTLV-I seropositivity on the outcome of pregnancy, on the identification of factors associated with perinatal transmission, and on maternal and child health. The National Cooperative Drug Discovery Groups (NCDDG) for the treatment of AIDS and the National Cooperative Vaccine Development Groups (NCVDG) are expected to be particularly suitable for international collaboration. In FY 1987, NIAID added 13 NCDDGs to the five established in 1986. One of the original NCDDGs collaborates extensively with a counterpart institution in the United Kingdom. NIAID will expand its current network of six general Vaccine Evaluation Units with NCVDGs within the next year. Proposals from U.S. institutions currently undergoing scientific review include vaccine collaboration with several Western European countries.

Intramurally, the NIAID Laboratory of Immunoregulation continues to collaborate with the Centers for Disease Control, the Institute of Tropical Medicine (Antwerp), and the Ministry of Health of Zaire on HIV infection and AIDS in that country. Known as Project SIDA, this landmark study of AIDS in Africa is now in its fourth year. To date, Project SIDA has identified more than 6,000 AIDS cases in Kinshasa with a 1:1.3 male to female ratio. In Kinshasa and elsewhere in Africa, HIV is predominantly transmitted by heterosexual contact rather than by male homosexuals or intravenous illicit drug abuse. The frequent use of unscreened blood donations to transfuse young children with severe anemia caused by malaria has been identified as a problem in Kinshasa and probably in other urban areas of Africa.

In adults, Project SIDA has identified high seroprevalence rates among spouses of AIDS patients, female prostitutes, and populations attending clinics for sexually transmitted diseases. The presence of genital ulcerations, history of oral contraceptive use, and failure to use condoms are statistically associated with heterosexual HIV transmission. Natural history studies have documented a 2 percent annual HIV seroconversion rate in the general population. To date, the progression from HIV-seropositivity to clinical disease is similar to that observed in the United States. The equal risk of HIV infection in adult men and women of childbearing age has resulted in frequent HIV transmission *in utero* or during birth. In HIV-infected mothers, maternal-infant transmission is associated with advanced clinical disease and immunologic impairment (e.g., reversed T4/T8 ratios). Maternal HIV infection also is associated with premature birth, low birth weight infants, and high death rates (11 percent) in the first 3 months of life.

In West Africa, NIAID has participated in serologic and virologic studies that have confirmed the presence of a second human retrovirus, currently referred

to as HIV-II. Future NIAID studies in Africa will continue to focus on:

- The natural history of HIV-I infection;
- The importance of HIV-II and other retroviruses in the pathogenesis of AIDS;
- Perinatal transmission;
- The safety and efficacy of childhood immunization programs; and
- Genomic changes of retroviral isolates over time and in different geographic regions.

In November 1986, NIAID, the National Cancer Institute (NCI), CDC, AID, and WHO convened a workshop on AIDS in Africa at the Regional Office of WHO for Africa in Brazzaville, People's Republic of the Congo, in which 73 African scientists from 38 countries participated. The workshop produced a series of technical recommendations to national authorities and WHO in the following areas:

- Epidemiology;
- Clinical case definition;
- Diagnosis and confirmatory tests;
- Handling of blood and blood products;
- Education of health professionals;
- Risk factors and prospective studies;
- Case management;
- Contact and family counseling; and
- Prevention of sexual transmission.

In June 1987, immediately before the Third International Conference on AIDS, NIAID convened a second 1-day workshop on AIDS in Africa to review the status of ongoing research projects and provide a forum for discussion of research opportunities and needs. The workshop identified the need to strengthen behavioral and social research to support and complement the epidemiologic research already under way or planned. As a result, NIAID and AID will hold a 2-day workshop on AIDS and anthropological research in Washington, D.C., in January 1988.

Asthma and Allergic Diseases Centers

NIAID initiated a network of domestic Asthma and Allergic Disease Centers (AADCs) in 1971 to study the etiology, pathogenesis, diagnosis, prevention, and treatment of allergic diseases and to incorporate advances in basic research to clinical investigation. The 11 current AADCs are located at the Brigham and Women's Hospital (Boston); the University of California/San Diego; Duke University Medical Center (Durham, North Carolina); Northwestern University Medical School (Chicago); the Mayo Clinic and Foundation (Rochester, Minnesota); State University of New York/Stony Brook; Rockefeller University/Cornell University Medical College (New York City); Scripps Clinic and Research Foundation (La Jolla); University of Texas/Dallas Health Science Center; Tufts University School of Medicine (Medford, Massachusetts); and the University of Wisconsin Medical School. Allergic problems under investigation at the AADCs include:

- Asthma;
- Skin disorders such as atopic dermatitis;
- Urticaria;
- Angioedema; and
- Allergic reactions caused by insect bites, foods, drugs, chemicals, airborne allergens, and infectious diseases.

Research on chemical sensitization, for example, has produced the national and global capacity to mobilize quickly in emergencies. Following the Bhopal disaster in India caused by leakage of methyl isocyanate, NIAID-supported investigators rapidly developed a human serum albumin conjugate of this highly reactive chemical with the potential for use as a biological marker for exposure to this substance.

Diarrheal Diseases, Including Cholera

In the United States, diarrheal diseases cause 4 percent of acute illnesses. Approximately 4 of the 8 million (50 percent) Americans who travel overseas each year develop traveler's diarrhea. In the developing world, however, diarrhea is the single leading cause of death in infants and young children.

During FY 1987, the NIAID-supported Center for Vaccine Studies at the University of Maryland participated in studies in Bangladesh that showed that three doses of a killed cholera vaccine given by mouth provided 85 percent protection for at least 6 months against naturally acquired cholera (*Vibrio cholerae*). A second cholera vaccine candidate developed with recombinant DNA techniques has proven safe in U.S. volunteers and has protected them against challenge with a variety of virulent strains of *V. cholerae*. Field studies with this CVD103 cholera vaccine are under way in Thailand in cooperation with Mahidol University.

NIAID-supported research at the University of Texas Medical School/Houston has documented that enteroadherent *Escherichia coli* are important causes of diarrhea in Mexican children in Guadalajara and

are second only to enterotoxigenic *E. coli* among pathogens isolated from pediatric patients. This study confirms earlier observations in Americans who developed diarrhea during or immediately after travel to Mexico. The Houston group continues to study the efficacy of bismuth subsalicylate (Pepto-Bismol) in the prevention of traveler's diarrhea. Earlier studies had shown that U.S. summer students in Mexico who took liquid bismuth subsalicylate had 60 percent less traveler's diarrhea compared with those who took a placebo. Routine use of the liquid preparation, however, required quantities too large to carry on long trips. A 1987 study published by the Houston-Guadalajara team evaluated the efficacy of bismuth subsalicylate tablets at two dosage levels. The higher dose (two tablets four times a day) was well tolerated and provided the same level of protection as the liquid form. The most common side effects were blackening of the tongue or stools and tinnitus.

In recently completed studies, trimethoprim, trimethoprim (T), trimethoprim-sulfamethoxazole (T/S), and ciproflavoxin (CP) were compared with each other and a placebo in the treatment of diarrhea in Americans visiting Guadalajara for short periods of time. T/S and CP (but not T or placebo) were effective in the treatment of mild, moderate, and severe cases of diarrhea. These studies are expected to provide a basis for the management of traveler's diarrhea in the future, comparison with other drug regimens, and the evaluation of new agents.

Rotaviruses have emerged as the single most important group of etiologic agents that produce severe diarrhea in infants and young children in both industrialized and developing countries. Until recently, there were only four human rotavirus serotypes (types 1, 2, 3, and 4).

Investigators in the NIAID Laboratory of Infectious Diseases (LID) have now identified two additional human serotypes whose VP7 gene has been sequenced and is significantly different from the known serotypes. In addition to defining the number of rotavirus serotypes, an effective strategy for immunization requires an understanding of the extent and duration of immunity to viral infection and disease.

NIAID has initiated a prospective study of Egyptian children who experienced one documented attack of rotavirus infection. To date, six of these children have experienced a second bout of rotavirus diarrhea. Three cases were caused by the same rotavirus serotype as the first episode; the other three were caused by another serotype.

Field trials with the attenuated rhesus rotavirus vaccine developed at NIAID have been carried out in the United States and are under way or planned in Chile, Finland, India, Pakistan, Sweden, and Venezuela. To date, the most promising results are from Venezuela, where vaccine efficacy was 93 percent in 1- to 5-month-old infants and 100 percent for severe rotavirus diarrhea in all age groups. The prevalent strain of rotavirus in Venezuela, however, was the same as the vaccine. By contrast, the rhesus rotavirus vaccine was not effective in situations where the prevalent rotavirus serotype differed from that in the vaccine. It appears, therefore, that serotype-specific immunity is necessary to confer protection. Efforts are now under way to develop a multivalent vaccine that will protect against all the human rotavirus serotypes. One approach to this problem has been to transfer rhesus rotavirus vaccine-attenuating genes to reassortant rotaviruses that bear the major neutralization protein (VP7) of serotypes 1, 2, or 4. In Phase I clinical trials, these reassortants are as attenuated and immunogenic as the rhesus rotavirus vaccine.

Pertussis Vaccine Development and Evaluation

Pertussis (whooping cough) is a highly communicable disease caused by the bacterium *Bordetella pertussis*. At the turn of the century, virtually every child acquired whooping cough, and several thousand deaths occurred every year, primarily in infants. Since the development of killed pertussis vaccine in the 1930s, the licensure of diphtheria-pertussis-tetanus toxoid (DPT) combined vaccine, and the widespread use of DPT vaccine in childhood immunization programs since the 1950s, reported cases of whooping cough in the United States have declined to 1,000–3,000 cases and 5–20 deaths per year. During the 1970s, however, immunization levels in Western Europe, Japan, and to a lesser extent the United States have declined because of concern about adverse reactions to the whole bacteria vaccine. Fortunately, modern biotechnology has made possible the development of improved vaccine candidates.

Efforts are under way at the NIAID Rocky Mountain facilities to use recombinant DNA techniques to isolate specific proteins from the toxin of *B. pertussis* that are associated with clinical disease. Cloned DNA fragments that contain the coding information for three structural subunits (S1, S2, and S3) of pertussis toxin produce an immune response and partial protection when administered combined with an adjuvant to mice. A search is under way also for the active site on the pertussis toxin in the hope that it can be inactivated so that it will not produce disease but still produce immunity.

For the past several years, NIAID-supported Vaccine Evaluation Units at Marshall University (West Vir-

ginia) and Vanderbilt University (Nashville) have studied the safety and antigenicity of the Takeda acellular pertussis vaccine manufactured in Japan (DPT-J) and licensed for distribution in the United States by Wyeth Laboratories. Takeda DPT-J vaccine has been found to be as effective as whole cell vaccine in inducing immune responses to diphtheria, tetanus, and pertussis in both older (4- to 6-year-old) and younger (6-month-old) children.

In February 1986, NIAID, AID, and the National Bacteriological Laboratory (Stockholm) initiated a randomized, double-blind, placebo-controlled comparison of two purified acellular Biken vaccines manufactured in Japan. The first vaccine contains both the LPF and FHA pertussis antigens; the second only LPF toxoid. The two vaccines have been administered at 6 and 8 months of age to 3,800 infants throughout Sweden. Because pediatric immunization rates are low in Sweden as a result of concern about toxic reactions to the whole cell DPT vaccine, the goal of the study is to determine the percentage reduction of pertussis in vaccinated children compared to placebo-vaccinated controls. The study also will measure the protective antibody response following vaccination and side effects to both acellular pertussis vaccines. The study is scheduled for completion in March 1988.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

NIAID conducts scientific exchange and collaborative research through a variety of mechanisms that range from direct scientist-to-scientist contact to formal agreements for cooperation at the highest level of government. These agreements may be negotiated at the presidential, Department of Health and Human Services (DHHS), or NIH levels. Agreements for bilateral cooperation in science and technology have multiplied in recent years as a result of recent advances in immunology, genetic engineering, molecular biology, biotechnology, and vaccine development. In FY 1987, the global AIDS emergency resulted in new bilateral activities with France, the Federal Republic of Germany, and Japan. At present, NIAID conducts or funds cooperative research under agreements with Brazil, China, Egypt, Finland, France, India, Italy, Japan, Poland, Spain, U.S.S.R., and Taiwan. In addition, NIAID staff and awardees conduct scientific exchange and collaboration with a total of 75 countries through normal scientific channels.

Abu Dhabi: NIAID organized a program for the Assistant Undersecretary of the Ministry of Health during the national infectious disease meetings in New York City. The discussions focused on community education and prevention of AIDS and cooperation in the development and evaluation of vaccines.

Argentina: During FY 1987, four Argentine Visiting Fellows worked in the NIAID intramural laboratories. The NIAID Laboratory of Immunoregulation (LIR) made arrangements to host a Guest Professor from Hospital Escuela (Corrientes) for 1 month in autoimmune and infectious diseases.

Australia: There were five Australian Visiting Scientists and two Visiting Fellows in NIAID laboratories in FY 1987. Intramurally, the NIAID Laboratory of Parasitic Diseases (LPD) is collaborating with the Department of Biochemistry, University of Victoria, to study the biochemical cytology of host-protozoal interactions in *Leishmania* and *Trypanosoma*. The ability to characterize the function of parasite surface membrane components may identify targets for immunodiagnosis and/or chemotherapy. A scientist from the Special AIDS Unit at Fairfield Hospital visited NIAID to explore mutual interest and mechanisms to collaborate in the molecular biology, cell biology, and pathogenesis of HIV-I.

Austria: In April 1987, the NIH and the Austrian Science Foundation (FWF) signed a 5-year Memorandum of Understanding for a Biomedical Research Exchange Program. Although the program supports Austrian scientists to visit the United States, only non-Federal scientists are eligible for funding to travel to Austria. Information on the FWF-NIH program has been circulated to NIAID intramural laboratories and extramural program administrators.

The University of Vienna Medical School and the NIAID Laboratory of Immunogenetics (LIG) and Laboratory of Immunology (LI) have reported the identification of a T3-associated gamma-delta T-cell receptor on Thy-1 + dendritic epidermal cell lines. The localization of these receptors in the skin may be of importance in understanding T-cell activation. Studies are under way using monoclonal antibodies (MAbs) as probes for T-cell activation. One Austrian Visiting Associate is currently in LI.

Bangladesh: During FY 1987, a senior scientist at the NIAID-supported Enteric Diseases Study Center at the Johns Hopkins University completed a long-term assignment in Dhaka and returned to Baltimore. The International Centre for Diarrheal Diseases Research/Bangladesh and the University of Maryland

at College Park continue to study the quantification, speciation, and ecology of *Vibrio cholerae* and other *Vibrio* organisms in aquatic ecologies in Bangladesh. Recent results include the use of fluorescent antibody methods to quantify *V. cholerae*, type 01, in village water supplies. This technique has found cholera vibrios in the water supply of two villages with cholera after bacteriologic cultures of water samples had been negative.

Belgium: The Institute de Medicine Tropical (Antwerp) is the major European participant in the NIAID-CDC-Ministry of Health of Zaire multidisciplinary Project SIDA, which is the first and largest study of the epidemiology, natural history, and risk factors for HIV-I and AIDS in Africa. LIR/NIAID is the intramural laboratory that developed and is now responsible for Project SIDA. Recent findings are summarized in the Highlights section.

Belgium is involved in two other intramural research projects. Smith-Kline-RIT and LID/NIAID have collaborated in the successful growth of Hepatitis A Virus (HAV), attenuation in monkey kidney tissue culture, cloning, and immunization of chimpanzees with the attenuated, recombinant DNA HAV vaccine. To date, the HAV vaccine has protected all immunized chimpanzees against challenge with the wild-type HAV.

The Mons State University and the NIAID Laboratory of Microbial Structure and Function (LMSF) are using recombinant DNA and chemical techniques to characterize the surface antigenic determinants of *Chlamydia trachomatis*. The gene encoding the major outer membrane protein (MOMP) has been subcloned into lambda gt-11 to express MOMP epitopes. Efforts are now directed toward identifying MOMP regions that contain epitopes specific for *C. trachomatis* type, species, and subspecies. Two Belgian Visiting Fellows and one Visiting Scientist were at NIAID in FY 1987.

Bolivia: In FY 1987, NIAID assisted an investigator in Cochabamba with the evaluation of the antiviral and antitumor properties of regenerator, a natural product derived from the *Calamus drago* palm, which is used in Bolivia as an astringent and for hemostasis. The Natural Products Branch, Division of Cancer Treatment, NCI, found modest killing effect in the KB cell system.

Brazil: NIAID-supported extramural investigators have been able to maintain a broad range of collaborative research projects with Brazil through the NIAID International Collaboration in Infectious Disease Research (ICIDR) Program and investigator-initiated grant applications. The ICIDR Program project awards to Cornell Medical College and Harvard University to conduct research in Brazil are now in their ninth years.

In FY 1987, for the first time in recent years, NIAID awarded a research grant to a Brazilian investigator (Federal University of Rio de Janeiro) to study the mode of action of trypanocidal cationic drugs. The Federal University of Goias and LPD/NIAID have addressed the problem of cross-reactions with other protozoa (e.g., *Leishmania*) in the immunodiagnosis of infection with *Trypanosoma cruzi* by using cloned 72- and 90-kilodalton glycoproteins of *T. cruzi* epimastigotes. These glycoproteins have been tested against sera from 141 patients, including 89 from Brazil, Bolivia, Mexico, and Nicaragua who were seropositive for chronic Chagas' disease. There was good binding with sera from patients with Chagas' disease and no cross-reaction with a variety of other conditions, including leishmaniasis, malaria, schistosomiasis, syphilis, toxoplasmosis, and *T. rangeli*, a nonpathogenic New World trypanosome.

The Oswaldo Cruz Foundation (FIOCRUZ) and New York University investigators have reported on epidemiologic studies conducted in 1983–85 to determine potential mosquito vectors of malaria in six areas of Para State in northern Brazil endemic for *Plasmodium falciparum* (16.7 percent) and *P. vivax* (10.9 percent). The immunoradiometric assay (IRMA) and enzyme-linked immunosorbent assay (ELISA) using falciparum or vivax malaria-specific antisporozoite MAbs were used to analyze more than 9,000 *Anopheline* mosquitoes for plasmodial infection. *P. falciparum* was found in *A. darlingi* (2.7–4.2 percent) and in *A. oswaldoi* in one study area. By contrast, the sporozoite antigen of *P. vivax* was found in diverse species such as *A. darlingi*, *A. triannulatus*, *A. nuneztovari*, and *A. albitarsis* at rates ranging from 0.9 to 12.0 percent. These last three species had not previously been considered vectors of significance in northern Brazil.

LPD/NIAID, George Washington University, and University of North Carolina investigators are collaborating with the Centro de Pesquisas Rene Rachou in Minas Gerais to define the macrophage deficiency in P strain mice that prevents the development of immunity to *Schistosoma mansoni* following vaccination with irradiated cercariae. The defect in macrophage function is caused by a fully recessive inherited trait controlled by only one or two genetic loci. They have documented that the level of macrophage activity is strongly associated with resistance to challenge with *S. mansoni cercariae*. This supports the hypothesis that activated macrophages

are the immune effector cells of resistance to *S. mansoni* in the mouse-irradiated-vaccine model.

Vanderbilt University also is collaborating with the Brazilian group in Minas Gerais to determine the effectiveness of antigenic preparations from *S. mansoni* schistosomula as immunogen in proliferation studies using peripheral blood mononuclear cells from Brazilian patients with chronic intestinal schistosomiasis. Living and fixed schistosomula were found to induce similar responses. The response to vesicular and tegumental components was very similar, although intact vesicles were more potent than those that were broken. This suggests that the manner in which membrane antigens are presented to antigen-processing cells is critical to the immune response.

NIAID-supported investigators at the University of Massachusetts and the University of Lowell have completed studies with the Centro de Pesquisas Rene Rachou to compare drug resistance in *S. mansoni* in Brazil and Kenya. This information is important because of increasing reliance on targeted chemotherapy of high-risk populations to control schistosomiasis. In Brazil, *S. mansoni* strains vary considerably in their responses to oltipraz, oxamniquine, and praziquantel but are much more susceptible to oxamniquine, the drug of choice, than Kenyan strains.

Labrea hepatitis (black fever) is an unusual type of severe hepatitis in the Amazon Basin that has been recognized clinically since the 1950s. In FY 1987, the Instituto Evandro Chagas, CDC, Mount Sinai School of Medicine, and LID/NIAID confirmed that infection with hepatitis delta virus (HDV) was an important cause of Labrea fever. In fulminant hepatitis cases, HDV superinfection of hepatitis B virus carriers was the most common explanation. Histopathologic features were identical to similar fulminant hepatitis cases caused by HDV in Colombia and Venezuela.

The Escola Paulista de Medicina (Sao Paulo) and the Uniformed Services University of the Health Sciences (Bethesda) have been involved in joint studies on the chemical properties and antigenic determinants among type II heat-labile enterotoxins of *E. coli*. Type II heat-labile enterotoxin (LT-II) from *E. coli* 41 isolated in Brazil has been purified and compared with prototype LT-II from *E. coli* SA53. The Brazilian LT-II belongs to a different subclass. Efforts are now under way to determine the LT-II characteristics of other *E. coli* isolated from Brazilian patients.

Bulgaria: In November 1986, the NIH and the Medical Academy of Bulgaria signed a Memorandum of Understanding for implementing a Biomedical Research Exchange Program. There are no NIAID activities under this arrangement currently.

Canada: Canadian scientists are involved actively in the NIAID intramural research program. In FY 1987, NIAID hosted three Canadian Visiting Fellows, two Visiting Associates, and one Visiting Scientist. Intramurally, the Laboratory of Clinical Investigation (LCI) and the University of Manitoba have collaborated on the evaluation of a highly sensitive and specific viral DNA probe to detect enteroadenoviruses types 40 and 41 in human stools. LCI/NIAID also has been involved in a multicenter study with the Killam Hospital for Children (Halifax) that showed that patients with presumed chronic active Epstein-Barr virus infection lack antibody to a component of the Epstein-Barr nuclear antigen (EBNA) complex encoded by the BanHI K fragment of viral DNA. This observation is being investigated in more detail.

The Laboratory Centre for Disease Control (Ottawa) and LIR/NIAID have been exploring whether the envelope proteins of HIV-I can be incorporated into a vaccine. Full-length and truncated HIV envelope proteins have been inserted into Baculovirus vectors and expressed in insect cell lines. Animals immunized with a 120-kilodalton HIV glycoprotein or recombinant HIV envelope produced high-titer antibodies that recognized the native HIV viral envelope. HIV-infected humans, however, do not produce protective antibody to the 120-kilodalton glycoprotein or the HIV envelope protein. The hypothesis that the lack of a human immune response may be caused by a misdirected immune response is under investigation.

The NIAID Laboratory of Molecular Immunology (LMM) and the Clinical Research Institute of Montreal collaborate on the mapping of genes involved in the transmission and transformation of tumor-inducing viruses (e.g., MuLV and mouse mammary tumor virus) in inbred mice. LPD/NIAID and the University of Montreal are involved in joint immunologic studies on the mechanisms of immune recognition and immunoregulation in filarial and nonfilarial diseases. Finally, LMSF/NIAID in Montana and the University of Edmonton in neighboring Alberta collaborate in the identification and characterization of the nonprotein surface proteolipids and capsular polysaccharides of *Neisseria gonorrheae*.

During FY 1987, two Canadian scientists were recipients of investigator-initiated grant awards. An investigator at the University of Manitoba has received grant support for 10 years to investigate the suppression of antibodies by tolerogenic conjugates.

The second grantee at the Montreal General Hospital is evaluating the INR (bacillus Calmette-Guérin [BCG]) gene as a probe to study host-parasite interactions.

In addition to these foreign awards, a growing number of domestic investigators have collaborative relationships with Canadian scientists. Perhaps the most widely publicized in FY 1987 was a joint study conducted in Kenya by LIR/NIAID, the University of Washington, the University of Manitoba, and the Nairobi City Council Sexually Transmitted Disease Clinic that identified genital ulcers as a risk factor for acquisition of HIV-I infection among clinic patients.

The Laboratory Centre for Disease Control (Ottawa) and the NIAID-supported Center for Vaccine Development at the University of Maryland also are involved in a multicountry study that has developed and is now evaluating a DNA probe to diagnose enterohemorrhagic *E. coli* belonging to 0157:H7 and other types associated with hemorrhagic colitis and the hemolytic uremic syndrome. The University of Calgary, the University of Colorado, and the Mount Sinai Hospital (New York City) have conducted similar studies of a DNA probe to use as an epidemiologic marker for molecular epidemiologic studies of *Pseudomonas aeruginosa* in burn wards and to trace the spread of hospital-acquired infections.

Elsewhere, the NIAID Vaccine Study Center at the University of Rochester is collaborating with several hospital and university groups in Quebec to study the immune response of splenectomized children to *Hemophilus influenzae,* type (Hib) PRP vaccine. These high-risk children mounted a protective response to Hib administered alone at monthly intervals for 3 months and to Hib administered simultaneously with 14-valent pneumococcal and bivalent meningococcal vaccines.

Chile: In June 1987, NIAID participated in a review of research proposals submitted by Chilean investigators to determine programmatic interest and identify likely U.S. collaborators. The American Embassy in Santiago generated the review as part of an effort to increase U.S.-Chilean scientific cooperation. Areas of potential interest were identified in American trypanosomiasis, hepatitis A, typhoid fever, and diarrheal disease. Scientists in both countries have been encouraged to develop the collaboration through normal scientific channels.

One Chilean Visiting Associate worked in LID/NIAID in FY 1987. LID/NIAID is planning to conduct field trials of rotavirus vaccines in Chile in the near future.

China: The U.S.-China Joint Committee on Science and Technology in Medicine and Public Health held its first meeting in 1979 in Beijing. Since then, NIAID has had primary responsibility for the Immunology Program Area, and CDC has had lead responsibility in infectious and parasitic diseases. The Protocol for Cooperation in Immunology emphasizes five broad areas:

- The immunology of infectious and parasitic diseases;
- Cancer;
- Diseases of the immune system, including primary immune deficiency diseases;
- Autoimmunity and allergy; and
- Skin and organ transplantation.

The Institute of Basic Medical Sciences (Beijing) is the NIAID immunology counterpart in China. Infectious hepatitis, influenza, malaria, and schistosomiasis are the four diseases selected for emphasis in the Infectious and Parasitic Diseases Program Area.

There are no U.S. supplemental funds earmarked for U.S.-China Cooperation, and the funding available to Chinese participants is finite. As a result, the U.S.-China Joint Health Agreement remains a landmark enabling document, but most bilateral cooperation takes place outside the formal program. Two NIAID staff members made formal site visits to Beijing, Shanghai, and Guangxi in February 1987 to review the status of ongoing and proposed vaccine studies for infectious hepatitis and plan for future collaboration.

For the past 8 years, the primary objective of the Immunology Program has been to use existing resources to provide research training opportunities in the United States for promising young Chinese scientists. In FY 1987, China continued to participate actively in the NIAID Visiting Scientist Program. Six Chinese scientists were long-term visitors at NIAID expense in LID, the Laboratory of Biology of Viruses (LBV), Laboratory of Molecular Immunity (LMI), and LMSF.

Infectious hepatitis has been the most active and productive area within the official bilateral program. This represents a joint effort by LID/NIAID and CDC in cooperation with the Institute of Virology (Beijing) and the Shanghai First Medical College.

During FY 1987, the University of North Carolina and the Institute of Epidemiology and Microbiology (Beijing) published several articles on their studies of rickettsiae in China. Laboratory-based work in the United States focused on the use of MAbs to analyze

T-cell-dependent and -independent antigens of *Rickettsia conorii*. The work in China consisted of a comprehensive review of the epidemiology and ecology of rickettsial diseases for the first time. Of the five rickettsioses endemic to China—murine typhus, Q fever, spotted fever group rickettsioses, epidemic typhus, and scrub typhus—the first three continue to represent important public health problems. *Coxiella burnettii* (Q fever), *Rickettsia tsutsugamushi* (scrub typhus), and spotted fever group (SFG) rickettsiae have been isolated from humans, arthropods, and animals. Doxycycline is the preferred treatment for murine typhus, epidemic typhus, and scrub typhus in China. Efforts are under way to identify and characterize SFG rickettsiae from human and tick sources in China.

Colombia: NIAID currently supports two ICIDR Program project awards to Tulane and Yale Universities to conduct collaborative research in Colombia. The Tulane collaboration began in 1959 under the ICMR Program and has continued since 1979 as an ICIDR award in collaboration with the Colombian Fund for Scientific Research (COLCIENCIAS). During FY 1987, the Tulane group described the results of enzyme electrophoretic studies of *T. rangeli* strains isolated from sylvatic and domiciliary reduviid (*Rhodnius prolixus*) bugs and humans living in a *T. cruzi* endemic area. *T. cruzi* demonstrated polymorphism to 13 different enzymes and 16 zymodenes. By contrast, *T. rangeli* from different geographic areas and ecologies was polymorphic for only one enzyme. Colombian *T. rangeli* zymodenes from sylvatic and more urban areas did differ somewhat but were much more similar phenotypically than stocks collected in Brazil and Chile.

Czechoslovakia: In May 1987, NIAID participated in an NIH survey to determine programmatic interest in bilateral cooperation under the terms of an agreement between the United States and the Czechoslovak Socialist Republic for Cooperation in Culture, Education, Science, and Technology. As a result, LVD/NIAID and the Institute of Sera and Vaccines (Prague) are exploring possible mutual interests in the development of vaccinia vector vaccine candidates. Extramurally, the University of Texas/San Antonio, the Institute of Parasitology (Bratislava), and Comenius University (Bratislava) have published a joint paper on protein-epitope phenotypic variation among fresh *Trichomonas vaginalis* isolates. The studies indicate that host immunologic responses influence the phenotype of infecting *T. vaginalis* populations.

Dominican Republic: Investigators at the University of South Florida have completed a survey of Bancroftian filariasis in the Dominican Republic. Foci of transmission persist in urban Santo Domingo, primarily in impoverished barrios where the prevalence of microfilaremia was as high as 9.8 percent. Lymphedema was documented in 3.8 percent of individuals with microfilaremia. Twenty-seven percent of dissected *Culex quinquefasciatus* and 15.4 percent of *Aedes aegypti*, the most prevalent mosquitoes, were positive for filariae. Rural filariasis is located primarily in the heavily populated sugar cane-growing areas and sugar-exporting ports. About 500,000 Dominicanos now reside in the United States, and imported cases of filariasis are certain to occur. *C. quinquefasciatus* and *Ae. aegypti* are common in the southeastern United States, but the last foci of *Wuchereria bancrofti* in Charleston, South Carolina, died out in the early part of this century.

Egypt: Initiated in December 1981, the NIAID-AID Regional Project on the epidemiology and control of vector-borne diseases in Egypt and Israel has been extended through December 1991. Research in Egypt is conducted through an NIAID contract with the Ain Shams Center for Research and Training in Vectors of Disease (Cairo). At present, research is under way in the following five disease complexes: filariasis, leishmaniasis, malaria, Rift Valley fever (RVF) and related arboviruses, and rickettsial diseases. Egyptian institutions involved in the project include the Ministries of Health and Agriculture, the Egyptian Academy of Sciences, and the Universities of Al Azar, Alexandria, and the Suez Canal. Participating U.S. institutions include Naval Medical Research Unit No. 3 (NAMRU-3/Cairo), CDC, University of Arizona, Columbia, Cornell, Eastern Virginia Medical College, Florida Medical Entomology Laboratory, University of Georgia, Harvard, Johns Hopkins, University of Maryland, Notre Dame, University of Virginia, Washington University, and Yale.

In 1986, AID, the Government of Egypt, and DHHS concluded arrangements for 2-year funding to maintain particularly meritorious P.L. 480 (Special Foreign Currency) projects. NIAID is responsible for one interim project with the Egyptian Organization for Biologics and Vaccines on the major childhood respiratory diseases in Egypt. The long-term objectives of the project are to participate in the development and evaluation of improved vaccines against *Bordetella pertussis, Hemophilus influenzae,* type b, *Neisseria meningitidis,* and *Streptococcal pneumoniae.* The 2-year interim activities will focus on:

- Improving the serodiagnosis of *B. pertussis*;
- Producing MAbs and polyclonal antibodies to identify surface molecules (e.g., LPF, FHA) and outer membrane proteins;

- Serotyping *B. pertussis* from Egyptian communities;
- Describing the natural history of mild and severe pertussis in Egypt; and
- Measuring pertussis vaccine efficacy in household contacts.

Efforts in the other three agents will be more modest and consist primarily of strengthening laboratory capacity for purification of capsular polysaccharides, serotyping of strains prevalent in Egypt, and improving vaccine formulation for use in Egypt. Longer-term funding is being sought from AID applied research programs in Egypt and Washington.

Surveillance for Rift Valley fever continues in Egypt but is concentrated on sentinel livestock in high-risk areas, school children born after the 1977–78 epidemic, and fever hospitals. During FY 1987, the Ministry of Agriculture and the Ain Shams Center investigated a small number of seropositive, unvaccinated sheep in the Aswan area. The antibody response was real, but not specific for RVF.

CDC is primarily responsible for an interim funding project on diarrheal diseases that is conducted at the Epidemiologic Study Center in Bilbeis, a Nile Delta village with a censused population of 25,000. LID/NIAID initially provided virology support to the center and the University of Texas/Houston provided bacteriology support. Although 44 percent of children had at least one bout with rotavirus by age 3, rotaviruses constituted only 3 percent of identified agents in children with diarrhea. As a result, Bilbeis was not a promising site for NIAID-supported rotavirus vaccine trials. By contrast, *Giardia lamblia* was the most common pathogen (44 percent), followed by heat-stable/ST- (15 percent) and heat-labile/LT-producing enterotoxigenic *E. coli*. Infection with *Giardia*, however, could not be correlated with clinical disease. This study resulted in a recommendation that *Giardia* asymptomatic infection not be treated in Egypt.

Ethiopia: NIAID provides ICIDR Program support to Wayne State University to collaborate with the Armauer Hansen Research Institute (Addis Ababa) on the improved diagnosis, delayed hypersensitivity reactions, peripheral neural autoimmune mechanisms, and viability of *Mycobacteria leprae*, the causative agent of leprosy. In FY 1987, the research group evaluated the inhibition ELISA and the direct dot-blot assay on nitrocellulose paper in the detection of a phenolic glycolipid (PGL-1) specific for *M. leprae* in the urine of patients with lepromatous leprosy. The direct dot-blot assay was much simpler and sensitive—as little as 3 ng of antigen could be detected in urine. Because *M. leprae* is currently detected by skin snips or biopsy, the ability to screen patients by a urine test to detect new cases or monitor the effectiveness of chemotherapy would be a significant development.

Finland: The Director of the NIAID Microbiology and Infectious Diseases Program (MIDP/NIAID) is the U.S. Coordinator for the DHHS-Ministry of Social Affairs and Health Memorandum of Understanding for the Development and Testing of Vaccines. LID/NIAID and the University of Turku are currently collaborating in the characterization of cloned hepatitis A virus cDNA to use in probes for the detection of the virus RNA in tissue cultures, liver tissue, and serum or fecal specimens. The University of Tempere is involved with LID/NIAID in efficacy studies of experimental rhesus rotavirus vaccine in Finnish infants.

France: Although most collaboration with France is conducted on a scientist-to-scientist basis, NIAID does coordinate the Immunology, Tropical Medicine, and Infectious Diseases Area of Cooperation established in FY 1985 within the Memorandum of Understanding between the NIH and the Institut National de la Santé et de la Recherche Médicale (INSERM). Priority NIH-INSERM research areas include: immunogenetics, immunology of parasites, and epidemiology of asthma and allergic diseases. During FY 1987, INSERM and the NIH agreed to develop AIDS as a separate and distinct Area of Cooperation.

In FY 1987, six French Visiting Fellows and two Visiting Associates worked in NIAID intramural research laboratories. The NIAID Laboratory of Immunogenetics and the Institut Pasteur (Paris) have maintained long-term exchange and collaboration in genetic studies on rabbit immunoglobulins and the characterization of rabbit MHC antigens and cell surface markers of rabbit lymphocytes. Recent experiments have resulted in the infection of HTLV-I transformed rabbit cell lines with HIV-I. LCI/NIAID and the Institut Pasteur have published a joint study that showed that mannosyl receptors on macrophages may represent a general mechanism for the clearance of *Aspergillus fumigatus* and other fungal mannans from the blood stream.

The NIAID Laboratory of Molecular Microbiology and the University of Bordeaux have been collaborating in basic studies on *Mycoplasma* organisms. The Laboratory of Persistent Viral Diseases (LPVD) in Montana and the Hôpital St. Louis (Paris) are exploring the role of endogenous and recombinant ret-

roviruses in anemia and erythroleukemia. LPVD/NIAID also has a project with Hôpital Cochin (Paris) on the structure and function of endogenous retroviruses expressed during differentiation. An endogenous mouse gene recently has been found to encode a unique retroviral envelope gp70 molecule associated with *in vivo* resistance to murine leukemia virus (MuLV)-induced erythroleukemia.

The NIAID Laboratory of Molecular Immunity (LMI), the Walter Reed Army Institute of Research, and INSERM (Flers) have conducted parasitologic and immunologic studies of experimental *P. falciparum* infection in nonsplenectomized chimpanzees. During the malarial infection, the chimpanzees developed a strong T-cell proliferative response to *P. falciparum*, and their monocytes showed enhanced phagocytic activity to malaria-infected red blood cells. The study suggests that cellular immune mechanisms, especially macrophage activation, help control falciparum malaria in nonhuman primates.

LCI/NIAID, the International Agency for Research on Cancer (Lyon), and other research groups are involved in multicenter studies on chronic, active Epstein-Barr virus infection. The University of South Florida, New York University, the Institut Pasteur, the University of Lille, and other centers are investigating the use of murabutide, a synthetic adjuvant, to induce biologically active antibodies without the presence of a protein carrier. Four antigens (*Streptococcus pyogenes* M protein, diphtheria toxin, hepatitis B surface antigen, and *P. knowlesi*) given to mice in murabutide-saline or Freund complete adjuvant produced high antibody levels to all four antigens. The induced antibodies appeared to be biologically active.

In other collaborative efforts involving NIAID awardees, the University of California/San Francisco, University of California/Davis, and the Institut Pasteur are following the natural history of HIV-I infection and risk factors for the development of AIDS in San Francisco men found to be seropositive in 1983–84. The rate of progression was strongly and independently associated with the number of T4 and T8 lymphocytes and the red blood cell count. T4 loss was continuous in men progressing to AIDS. The projected portion of HIV-positive men progressing to AIDS in 5 years is 30–35 percent.

The upsurge of tick-borne diseases in the Mediterranean Basin in recent years has prompted an increase in Franco-American cooperation in this research area. The University of North Carolina, in cooperation with two clinical groups in Marseille, has investigated the pathogenesis of severe hemolytic anemia in an Algerian patient with Mediterranean spotted fever. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was found in the patient and his family. The hemolysis occurred before antibiotic treatment. The likely explanation for the hemolysis is increased rickettsial activity caused by defective host defense. In a second study, CHU la Timone (Marseille) and the New York State Department of Health found that the sera of patients with syphilis cross-react with sera from patients with Lyme disease, as a result of *Borrelia burgdorferi*, a recently described tick-borne spirochete disease prevalent in the eastern United States. The cross-reaction was discovered when a percentage of U.S. patients with well-documented Lyme disease also were found to have positive VDRL screening and FTA-ABS confirmatory tests for syphilis. The New York patients were negative on RPR and MHATP tests for syphilis. The French group provided MHATP-positive syphilis patients to be tested for antibody to *B. burgdorferi*, which has not been documented in France. Nearly 50 percent (40 of 82) of French patients with syphilis showed a positive response as a result of IgG to *B. burgdorferi*.

Gambia: LPD/NIAID has conducted collaborative studies in malaria with the Medical Research Council Laboratories in Gambia for a number of years. Recent collaboration has focused on the biology and immunogenicity of malaria sporozoites. During FY 1987, LPD/NIAID, NCI, and Scripps investigators prepared a series of 29 synthetic overlapping peptides of the immunodominant region of the *P. falciparum* sporozoite in order to determine the specific domains recognized by T cells. The peptides were then tested *in vitro* for blastogenic activity with lymphocytes from patients immune to malaria from a holoendemic area of Gambia. Blastogenic responses occurred against a relatively restricted site of the circumsporozoite antigen. Since T cells are important in the development of protective immunity, this study provides encouragement that a circumsporozoite malaria vaccine may be feasible. LPD/NIAID, NCI, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Gambian Medical Research Council Laboratories also are investigating the pathogenesis of vascular sequestration in falciparum malaria. The study subjects were patients presenting with falciparum malaria in Gambia. Their cultured, parasitized erythrocytes bound to thrombospondin, an endothelial receptor. Binding, however, was not increased in two patients with cerebral malaria. The results support the hypothesis that specific binding to an endothelial receptor (possibly thrombospondin) is important in the vascular sequestration observed in falciparum malaria.

Federal Republic of Germany: During FY 1987, NIAID and the Federal Ministry for Research (Berlin) agreed to initiate a new joint area of research in AIDS under the terms of the Bilateral Cooperative Agreement for German-American Cooperation in Health Research. To develop the frame of reference for cooperation, the NIAID Director visited the Federal Republic of Germany in July 1987, and a German AIDS delegation visited Bethesda and Baltimore in November 1987.

In FY 1987, there were two German Visiting Fellows and two Visiting Associates in NIAID laboratories.

Greece: LID/NIAID and the National Center for Viral Hepatitis (Athens) have developed an expanding program of cooperation over the past several years. During FY 1987, the activities included investigation of a common source epidemic of hepatitis A virus (HAV) in an institution for young children. The study revealed that an accurate prediction of HAV attack rate required a complete battery of screening tests for anti-HAV in serum and HAV in stools. Immunoglobulin administration had no effect on the incidence of clinical hepatitis in the late incubation period. A second project studied 182 asymptomatic Greek carriers of hepatitis B surface antigen (HBsAg) who were heterosexual partners of patients with acute hepatitis B (HBV) and compared them to matched controls. The project found that:

- There is a positive correlation between the presence of HBV DNA in serum and sexual transmission of HBV;
- HBV DNA is a better indicator of infectivity than HBeAg/anti-HBe; and
- The detection of HBV DNA in serum identified carriers with high infectivity and high risk of transmission to their sexual partners.

Haiti: NIAID is very active in collaborative studies on HIV-I infection and AIDS in Haiti. In a retrospective study by the Cornell-GHESKIO group of sera collected during a 1977–79 dengue fever epidemic, none of 191 specimens were HIV-I positive compared to 1.8 percent (6 of 329) healthy urban adults in 1986. This suggests that HIV-I was introduced into Haiti relatively recently. A Johns Hopkins-Tulane study compared the prevalence of HIV-I antibody in pregnant Haitian women in 1982 and 1986. In an impoverished slum area, married women had a higher (11.5 percent) prevalence rate than unmarried (4.5–7.6 percent) women. Seroprevalence was highest (11.2 percent) in the 20- to 24-year-old age group. The overall prevalence of 8.4 percent in 1986, however, was not significantly higher than the 7.6 percent rate observed from the same study population in 1982. The explanation for the relative stability of HIV-infection rates in this high-risk group of Haitian women requires further investigation.

A number of recent joint studies deal with the clinical manifestations, complications, and co-factors associated with AIDS in Haiti. The Cornell-GHESKIO group has observed that nearly one-half of AIDS patients have intensely pruritic skin lesions that are occasionally seen in seropositive spouses, but not in other family members or friends. AIDS patients with and without prurigo do not differ from each other in demographic characteristics or in laboratory parameters.

LPD/NIAID, Cornell, and GHESKIO have explored whether infection with *P. falciparum* malaria may be a risk factor for AIDS. Although rural residence was associated with malaria seropositivity and urban residence with HIV seropositivity, malaria and HIV seropositivity were *inversely* associated with each other. The Cornell-GHESKIO team also has investigated the clinical manifestations and treatment of *Isospora belli,* a protozoal intestinal parasite rarely documented in U.S. AIDS patients but common in Haiti. About 15 percent (20 of 131) AIDS patients have documented isosporiasis characterized by chronic watery diarrhea and weight loss. Recurrent, symptomatic isosporiasis developed in 47 percent of the affected patients. Patients with *I. belli* infection responded promptly to therapy with trimethoprim-sulfamethoxazole.

The Tulane ICIDR award has supported immunologic studies on filariasis in Haiti for several years. Ongoing studies on the immunobiology of Bancroftian filariasis in Haiti have identified a significant number of individuals who, contrary to the usual suppressed *in vitro* cellular responsiveness to filarial antigens, are microfilaremic but "respond" to filarial antigens. This cellular reactivity in "responders" is persistent and may represent a stable phenotype in a subset of patients. Longitudinal studies are planned to determine whether microfilaremic responders and nonresponders differ with respect to the development of chronic lymphatic disease.

Since the recognition of AIDS, cryptosporidiosis has emerged as a common cause of diarrhea in AIDS patients in Haiti and elsewhere in the tropics. This observation has stimulated a search for *Cryptosporidia* oocysts in the stool of infants and children with diarrhea. The Cornell group, in association with the Department of Pediatrics, State University Hospital of Haiti (Port-au-Prince), has used a modified acid-fast stain to examine the diarrheal stools of 824 Haitian children less than 2 years of age. Oocysts were

found with equal frequency in a rural dispensary (16.3 percent) and an urban hospital (17.5 percent). Cryptosporidiosis occurred more commonly in children more than 6 months old and was rarely seen in infants who were exclusively breast-fed. Diarrhea caused by *Cryptosporidia* could not be distinguished from other organisms. *Cryptosporidia* oocysts were not found in asymptomatic household contacts. Cryptosporidiosis therefore appears to be an important cause of diarrhea in children in Haiti.

India: NIAID has been actively involved in collaborative research with India for more than 25 years. Initially, this collaboration was carried out with P.L. 480 funds, which ceased to become available for new awards in October 1985.

NIAID participates in two bilateral programs: the Indo-U.S. Subcommission on Science and Technology, which was reactivated in 1978, and the Indo-U.S. Science and Technology Initiative, initiated in July 1982. Rupee funds are available to both programs from the U.S.-India Capital Fund, established in 1985 to replace the P.L. 480 funds.

The Indo-U.S. Working Group on Health of the Subcommission on Science and Technology met in New Delhi in November 1987 to review progress and reexamine priority areas. The mutually agreed-upon areas for collaboration within the NIAID research mission are:

- Acute respiratory diseases;
- Allergy and immunology;
- Diarrheal diseases;
- Filariasis;
- Guinea worm;
- Hepatitis;
- Leishmaniasis;
- Leprosy;
- Malaria;
- Sexually transmitted diseases, including AIDS;
- Streptococcal diseases;
- Tuberculosis; and
- The Vaccine Action Program.

In July 1982, the President of the United States and the Prime Minister of India agreed to establish a second bilateral science and technology program, the Indo-U.S. Science and Technology Initiative (STI), now named the Reagan-Indira Gandhi Initiative. At present, both the Indo-U.S. Subcommission on Science and Technology and the Indo-U.S. STI programs rely on the NIAID regular, domestic research budget for dollar expenses.

In FY 1987, 10 Indian scientists participated in the NIAID intramural program as Visiting Fellows and 5, as Visiting Associates. The host NIAID laboratory provides their stipends, insurance, and family allowances.

Allergy and Immunology: Cooperation in this area has been difficult to initiate. The subcommission has now encouraged an LCI/NIAID, Tufts, University of California/San Diego, and Indian Institute of Science in Bangalore (IISc/B) proposal to conduct comparative studies on the immediate hypersensitivity and pathogenesis of allergy to *Parthenium*, a ragweed-like plant that is toxic to animals, produces contact dermatitis in India, and has been introduced into the southeastern United States. In addition, an NIH Division of Research Resources and NIAID Laboratory of Immunopathology (LIP) proposal to study the genetics of wild mice in India is under development.

Filariasis: Of the five NIAID filariasis projects, one is under the subcommission and four under the STI. The subcommission project between the LPD/NIAID and the Indian Council for Medical Research (ICMR) Tuberculosis Research Center (TRC) in Madras began in 1978. In FY 1987, the project demonstrated the presence of high-molecular-weight glycolipid antigens to *Wuchereria bancrofti* circulating in the blood of patients with filariasis. MAbs have been generated against this glycolipid antigen and are being evaluated for sensitivity and specificity in the immunodiagnosis of filariasis. A subset of patients with filariasis have been found to have T cells that exert an immunosuppressive effect on *W. bancrofti.* A study on the activity of immune cells in lymphatic tissues from patients with elephantiasis undergoing reconstructive surgery is under way. Clinical trials on the effectiveness of a single oral dose of Ivermectin, a new antifilarial drug, with DEC, the traditional treatment, are being conducted.

Hepatitis: The single NIAID hepatitis project between LID/NIAID and the ICMR National Institute of Virology (Pune) has been supported for the past 3 years by a P.L. 480 grant and deals with the epidemiology and etiology of infectious hepatitis agents in India. The current emphasis is on non-A, non-B hepatitis, which, in India, is water-borne, frequently causes large epidemics in older children and adults, and is associated with particularly severe illness and death in pregnant women. The epidemiology and clinical manifestations of this problem in India in-

dicate that the etiologic agent(s) is distinct from those in the United States. LID/NIAID has identified virus-like particles from Indian patients, but attempts to cultivate the non-A, non-B hepatitis agent in chimpanzees and marmosets have failed. During the past year, the immunoadherence hemagglutination rapid diagnostic test has been established in Pune and used effectively to determine that the recent outbreak of hepatitis in Ahmedabad was caused by non-A, non-B hepatitis.

Leishmaniasis: LPD/NIAID and the ICMR Rajendra Prasad Research Institute in Patna (Bihar), where visceral leishmaniasis (kala-azar) is epidemic, have developed a protocol to study the epidemiology and immunology of kala-azar and post-kala-azar dermal leishmaniasis. Kala-azar is almost always fatal if not recognized and adequately treated. The joint effort will bring the powerful tools of modern immunology and biotechnology to bear on this important public health problem. The Bihar epidemic also represents a unique opportunity to study post-kala-azar dermal leishmaniasis, which is a rare phenomenon in most of the world but has been reported following treatment in 20 percent of Indian patients.

Leprosy: Seven of the eight active Indo-U.S. leprosy projects are in the STI. The subcommission project at the Foundation for Medical Research in Bombay (FMR/B) is funded by a P.L. 480 grant and is concerned with the use of a radioisotope metabolic precursor of dapsone to screen drugs for activity against *Mycobacterium leprae* and to detect the emergence of dapsone resistance.

The Rockefeller University and the All India Institute of Medical Sciences (AIIMS) group have completed their project on the role of dendritic cells in antigen-induced lymphoproliferative responses in leprosy. The contributions of this project included:

- Standardization and quantification of methods to purify human dendritic cells in blood;
- Documentation that human dendritic cells are potent accessories in the enhancement of T-cell lymphoproliferative responsiveness in patients with lepromatous leprosy;
- Identification of the H37 RA antigen of *M. tuberculosis* as an immunostimulant in lepromatous leprosy patients; and
- Confirmation that antigen-reactive T cells persist in many lepromatous leprosy cases.

Israel: During FY 1987, one Israeli Visiting Fellow and two Visiting Scientists worked in the NIAID intramural program. At present, LMM/NIAID collaborates with the Hebrew University in the development of molecular probes for the detection of *Mycoplasma genitalium.* A radioactive DNA probe specific for *M. genitalium* can detect 0.1 ng of DNA (approximately 1,000 organisms) in blot hybridizations. LPD/NIAID collaborates with the Weizmann Institute of Science in the development and evaluation of nuclear probes for *E. histolytica* and with the Technion Institute of Technology in the biochemistry of host-parasite interaction in protozoal parasites.

During FY 1987, NIAID supported four research grants awarded to Israeli investigators. Three were to the Weizmann Institute of Science on the IgE-receptor-calcium channel complex on basophils; the phagocytosis of bacteria via bacterial surface lectins; and the restoration of chemotaxis in bacterial cell envelopes. The Hebrew University is the recipient of the fourth grant, on pores induced by malarial parasites in the membranes of human red blood cells.

Jamaica: In February 1987, NIAID participated in an NIH orientation for two senior Jamaican health officials in epidemiology and infectious diseases.

Japan: NIAID is involved in two bilateral initiatives with Japan. They are the U.S.-Japan Cooperative Medical Sciences Program (USJCMSP) and the U.S.-Japan Science and Technology Agreement for Non-Energy Cooperation. The USJCMSP, established in a 1965 Act of Congress, is unique among bilateral programs because it is devoted to health problems of importance to Asia, not the two participating countries. The USJCMSP represents a joint effort between the Department of State (DOS), which is responsible for foreign policy, and DHHS, which is responsible for the scientific elements. NIAID has provided the Secretariat for the USJCMSP since 1968. Senior scientists from both countries are delegates to the Joint Committee, which oversees the USJCMSP. Panels of experts have been established in the United States and Japan in mutually agreed-upon disease areas. At present, there are panels in leprosy, tuberculosis, cholera, hepatitis, parasitic diseases, viral diseases, environmental mutagenesis and carcinogenesis, and malnutrition as well as an immunology board, established in 1981. In response to a request by the Government of Japan, the Joint Committee agreed in July 1987 to establish a new panel on AIDS. Ordinarily, the Joint Committee and Panels meet once a year, alternating countries. A scientific conference at which recent research advances are discussed is organized at each panel session.

The Non-Energy Agreement was established by the President of the United States and the Prime Min-

ister of Japan to promote cooperation in areas of research not related to the oil crisis and not included in other bilateral programs. In this second initiative, NIAID has lead responsibility for vaccine development, antivirals, and recombinant DNA research.

Japan had 18 participants in the NIAID Visiting Program in FY 1987 as Fellows (11), Associates (5), and Scientists (2)—the largest national group. There were at least eight active intramural projects with six NIAID laboratories.

In March 1987 the Public Health Service's Interagency Group to Monitor Vaccine Development, Production, and Usage published a report of its December 1986 visit to Japan to gather information on acellular and whole cell pertussis vaccines developed and in use there. Since the introduction of acellular pertussis vaccines in Japan in 1981, there have been less frequent vaccine reactions, high levels of protection, and a decline in reported cases of pertussis.

The visit provided useful information on additional studies needed to be done before licensure of acellular pertussis vaccines in the United States.

Osaka University participated in a study involving six U.S. groups on the molecular epidemiology of live, attenuated varicella (chickenpox) vaccine in children with leukemia and in normal adults. The cooperative study has shown through restriction endonuclease analysis of varicella DNA that the vaccine does protect against severe chickenpox in leukemic children susceptible to chickenpox but that the vaccine virus can establish latency and reactivate as herpes zoster.

Kenya: An NIAID-supported investigator at the University of Massachusetts has completed studies in Kenya on the drug resistance of *Schistosoma mansoni* that demonstrated that Kenyan strains were more resistant to oxamniquine than *S. mansoni* from Brazil.

During FY 1987, LIR/NIAID staff initiated joint studies with Kenyan counterparts on the epidemiology and risk factors for HIV-I and AIDS. In brief, genital ulceration has been identified as a risk factor for HIV infection in Kenya. A second study by the University of Nairobi, LIR/NIAID, the University of Washington, the University of Manitoba, and the Institute of Tropical Medicine (Antwerp) is investigating the congenital transmission of HIV. More than 2,000 women in labor have been screened for HIV antibody at the Pumwani Maternity Hospital in Nairobi. The outcome of pregnancy is being evaluated in 62 seropositive mothers and 124 matched normal controls. Infants born to HIV-positive mothers had more frequent palpable lymph nodes but were identical in birth weight, gestational age, and Apgar scores. All 53 infants born to seropositive women had cord blood HIV IgG antibody, and 9 of 53 (17 percent) had IgM antibody. Prospective studies are under way to determine if cord blood IgM HIV antibody is an accurate marker of *in utero* HIV infection.

Lebanon: During FY 1987, the NIAID-AID regional project on the epidemiology and control of vectorborne diseases in the Near East and U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)/Ft. Detrick assisted the American University of Beirut in determining the significance of a survey in which 11 of 277 (4.0 percent) samples of sera from Beirut and South Lebanon tested for Rift Valley fever were positive by the hemagglutination inhibition test. Reference studies indicated that the seropositivity was not caused by Rift Valley fever but by a closely related Phlebovirus.

An NIAID awardee at Youngstown State University and a Lebanese investigator have published on the biochemical identities and differences among 20 species and subspecies of *Leishmania* tested by three enzyme systems (e.g., glucose phosphate isomerase, mannose phosphate isomerase, and phosphogluconate dehydrogenase). Most *Leishmania* could be identified from data of these three enzymes, provided 10^6 power cells were available. Cellulose acetate electrophoresis data for 20 enzymes from more than 300 Old and New World strains also were analyzed. The biochemical data suggest that similarities and differences among *Leishmania* can be quantified as they have for other species.

Mexico: At present, NIAID has three active intramural projects with Mexican investigators. LCI/NIAID, LPD/NIAID, and Duke University are collaborating with the Institute of Public Health and Tropical Diseases in studies on diffuse cutaneous leishmaniasis (DCL). At least six newly recognized DCL cases have been documented in three distinct geographic areas of Mexico. Cutaneous leishmaniasis is prevalent in one area but not the others. Most of the Mexican patients have been or will be evaluated immunologically and treated in the NIH Clinical Center. Some of the DCL isolates have been typed as belonging to the *L. mexicana* complex. Efforts to identify the immunosuppressive population of lymphocytes in DCL patients have not been successful thus far. LI/NIAID and the National University of Mexico are collaborating in studies on the ontogeny and differentiation of rabbit immunoglobulins and the expression of immunoglobulin genes.

Netherlands: Two Dutch Visiting Fellows were at NIAID in FY 1987. NIAID also made a foreign individual research training award to the Netherlands Cancer Institute on the structure and function of telomeres in trypanosomes. Extramurally, CDC, Emory University, the Whitehead Institute for Biomedical Research, the Massachusetts Institute of Technology, and the Royal Institute for Public Health and Hygiene (Bilthoven) conducted a multicenter study that showed that *M. leprae, M. tuberculosis,* and the vaccine strain of *M. bovis* BCG share an immunoreactive protein antigen. In addition, the Royal Tropical Institute (Amsterdam) is a participant with the University of Washington and other centers on the characterization of antibody-reactive epitopes on the 65-kilodalton protein of *M. leprae.*

Norway: In FY 1987, there was one Norwegian Visiting Scientist in NIAID laboratories. NIAID organized a program of visits in Bethesda for the person in charge of AIDS cases in the Ulleval Hospital (Oslo). NIAID awardees at the University of Rochester, the Food and Drug Administration, Walter Reed, and the National Institute of Public Health (Oslo) have conducted a joint study on the genetic relationships and clonal population structures of *Neisseria meningitidis,* serotype 2. The study concluded that the recent failure to find pathogenic strains of serotype 2a in North America and South Africa is the result of clone replacement rather than evolutionary modification of the serotype protein.

Pakistan: NIAID has recently developed institution-to-institution contact with the Aga Khan University (Karachi) through former participants in the Visitors Program and Pakistani-Americans who have joined the faculty. There are two new intramural projects. LPD/NIAID and Aga Khan University have initiated a P.L. 480 project to assess clinical filariasis and the parameters associated with transmission in Pakistan. LID/NIAID has developed a second P.L. 480 project that will take advantage of the Uniformed Services University of the Health Sciences' cooperative program with the Pakistan Army Medical College (Rawalpindi) to study non-A, non-B and hepatitis delta virus infection in military recruits and troops.

Panama: In November 1986, LPD/NIAID staff participated in a visit to Panama and the Gorgas Memorial Laboratory to plan a trial of Ivermectin in human hookworm infection. Because the Gorgas Memorial Institute, which is responsible for the Gorgas Memorial Laboratory, is incorporated in the United States, awards to the institute are technically not foreign awards.

Peru: During FY 1987, there was one Visiting Associate from Peru in the NIAID intramural laboratories. Virtually all NIAID collaboration in Peru, however, results from the ICIDR Program project awarded in 1984 to Johns Hopkins University and the University of Maryland to collaborate with the Alexander von Humboldt Institute of Tropical Medicine at the Cayetano Heredia Peruvian University (UPCH) in Lima in research on bacterial diarrheal diseases, particularly shigellosis and typhoid fever.

Poland: During FY 1987, there were two Visiting Fellows from Poland in NIAID laboratories. As a result of a return toward normalization of U.S.-Polish contacts in science and technology, NIAID program staff reviewed three P.L. 480 projects that had been suspended for several years. NIAID has recommended the reactivation of a very productive project between the Copernicus School of Medicine (Cracow) and Yale University on mechanisms of contrasuppression in the mouse.

Rwanda: During FY 1987, NIAID made a commitment to fund the University of California/San Francisco to investigate HIV infection and AIDS in women and children in Rwanda. The contract proposal had been developed in response to a U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) announcement and deemed scientifically meritorious. Referral was made to NIAID because the area of the study was outside the USAMRIID research mission.

Seychelles: During FY 1987, a medical epidemiologist from the Ministry of Health visited NIAID to develop a cooperative study on asthma.

Sudan: LPD/NIAID staff visited the ICIDR in FY 1987 to evaluate the accuracy of ultrasonography in the noninvasive diagnosis of Symmer's pipe-stem hepatic fibrosis in the livers of Sudanese patients with advanced schistosomiasis. Ultrasonography correctly predicted the presence or absence of Symmer's fibrosis in all 28 patients tested who subsequently underwent surgery at the University of Khartoum. In a community-based village survey, 13 percent of the population had evidence of Symmer's fibrosis on ultrasonography. This is well above the 3 percent figure diagnosed on the basis of liver size and texture on physical examination.

LIR/NIAID scientific and technical staff traveled to Sudan in March 1987 to participate in a 3-day symposium on AIDS organized by the National AIDS Committee, help organize surveillance studies for HIV-I infection and AIDS.

Sweden: In October 1986, NIAID hosted a Swedish delegation from the Ministry of Health and Social Affairs to discuss research opportunities in AIDS and coordination of AIDS research efforts.

LID/NIAID has three and LMSF/NIAID one active intramural project with Swedish investigators. LID/NIAID and the Karolinska Institute cooperate in studies concerned with characterization of the fusion glycoprotein of respiratory syncytial virus and the human immune response to this virus infection or vaccination. LID/NIAID also collaborates with the University of Umea on field trials of experimental rhesus rotavirus vaccines in Swedish infants and children. LMSF/NIAID and the Karolinska Institute are investigating the nonprotein surface constituents of *Neisseria gonorrheae* to determine their role in the pathogenesis of disease.

With co-funding from AID, NIAID has awarded a research contract to the National Bacteriological Laboratory (Stockholm) to conduct an efficacy trial of two acellular pertussis vaccines. During FY 1987, the Baylor College of Medicine and the University of Goteborg have analyzed the pyelonephritis-associated pilus (PAP) operon from different geographic strains of *E. coli*. The PAP operon encodes the major mannose-resistant hemagglutinating adhesion of *E. coli* and contributes to colonization of the urinary tract. U.S. and Swedish isolates shared some identical PAP fragments and restriction fragments, but others were geographically unique. The University of Colorado and Danderyd Hospital have carried out genetic mapping studies of the structural gene for *Pseudomonas aeruginosa* phospholipase C (PLC), a possible virulence factor for *P. aeruginosa*. The study has shown that phospholipase C is located in the same area as the structural genes for exotoxin A and elastase.

Switzerland: One Swiss Visiting Fellow and one Visiting Scientist worked at NIAID in FY 1987. Intramurally, LCI/NIAID and the Canton Hospital (Basel) collaborate on studies of neutrophil function and phagocytosis in health and disease. The University of Geneva participates in LI/NIAID projects on allotypes and the ontogeny and differentiation of cells in the immune system of the rabbit.

Extramurally, NIAID-supported investigators at Cornell Medical College and the Institute for Microbiology and Hygiene (Basel) have been able to achieve long-term culture of *Toxoplasma gondii* cysts *in vitro* in mouse astrocytes by intermittent addition of gamma-interferon to the culture media. This model will be useful to produce antigens to *T. gondii* cysts and bradyzoites and to measure the effects of antimicrobial agents and immunomodulators on the viability of intracellular *T. gondii* parasites. A second grantee at the University of Washington, CDC, and the University of Zurich have joined forces to evaluate the use of purified *Echinococcus multilocularis* antigens for the screening, diagnosis, and clinical evaluation of alveolar hydatid disease in Alaskan Eskimo populations. The Swiss Em2 antigen was compared with whole *E. granulosus* hydatid cyst fluid. The Em2 ELISA test picked up 13 positive reactors in 998 persons screened compared to four in the EgF system. The Em2 ELISA is superior in sensitivity and clinical correlation but did not help in the evaluation of chemotherapy or distinguish active from inactive infections. Rockefeller University and Ciba-Geigy (Basel) have used a rabbit model for experimental pneumococcal meningitis to document that ampicillin-induced bacterial lysis and inflammation of the meninges is prevented by the simultaneous administration of cyclo-oxygenase inhibitors, which are nonsteroidal anti-inflammatory agents.

Investigators at the University of Maryland and Nestec (Vevey) have examined the effectiveness of an oral preparation of milk immunoglobulin concentrate as a prophylactic agent against enterotoxigenic *E. coli*, the most common cause of traveler's diarrhea. In a related study, the University of Zurich and the University of Texas/Houston evaluated the efficacy and side effects of six agents to treat traveler's diarrhea. More than 2,500 travelers to a variety of developing countries were randomly assigned in a double-blind study to receive one of six agents or a placebo to be taken only if diarrhea occurred. Thirty-one percent of travelers experienced diarrhea. After four hours, 41 percent taking loperamide were relieved of symptoms compared with 11–23 percent for the other agents or the placebo. Antimicrobial agents, however, were most effective for the small group (94) with dysentery. Minor side effects were noted with all the modalities.

Thailand: The United States and Thailand signed an Agreement for Cooperation in Science and Technology in April 1984, but NIAID carries out no bilateral activities under its terms. During FY 1987, New York University, Michigan State University, and Mahidol University reported that in Thai patients with falciparum malaria, there was no clear correlation between inhibition by sera of Fc receptor-mediated phagocytosis by human monocytes. This is in contrast to results from holoendemic areas of Gambia where phagocytosis did occur. The difference may be caused by host immune responses in Asia and Africa.

Trinidad and Tobago: LIR/NIAID has collaborated with the University of the West Indies/Port-of-Spain to investigate the hypothesis that genetic differences may explain the predominance of AIDS observed in Trinidadians of African origin compared to Trinidadians of Asian origin. Although each group constitutes 41 percent of the total population, 133 of the first 144 AIDS cases occurred in persons of African or mixed African descent. Other risk factors (e.g., male homosexuality, intravenous drug abuse) are similar in both groups. Initial immunogenetic studies indicate that HLA Dr 5 occurs in 25 percent of healthy black Trinidadians, but in no Asian Trinidadians studied. In addition, HLA Dr 1 and HLA Dr w6 are much more frequent in African than Indian populations. Although there are other explanations for this striking difference (e.g., earlier introduction of HIV-1 into Trinidadians of African stock, urban residence/lifestyle of Afro-Trinidadians compared to Indo-Trinidadians), these genetic differences will be investigated further.

Turkey: In April 1987, NIAID hosted a Turkish health delegation from the Ministry of Health and Social Assistance and Antalya University to explore future collaboration in malaria and AIDS.

United Kingdom: During FY 1987, the Secretary of State for Social Welfare and the Chief Medical Officer, Department of Health and Social Security; the Secretary of the Medical Research Council; and a Parliamentary Delegation visited NIAID on fact-finding visits on AIDS and NIH research policy.

The NIAID Visiting Program hosted seven English Fellows and two Associates in FY 1987. There were also six collaborative projects by four intramural laboratories. LCI/NIAID and the University Hospital (London) are conducting studies on the heterogeneity of human neutrophils as measured by chemotactic responses, Fc receptor-mediated rosetting, and monoclonal antibodies. LI/NIAID and Southampton General Hospital have completed their joint investigation of immunologic studies of guinea pig L2C leukemia. LPD/NIAID collaborates with the University of Edinburgh to study the genetic and physiologic factors that influence the vectorial capacity of *Anopheline* mosquitoes and the molecular genetics of *P. falciparum* in order to identify linkage groups and genes that affect drug susceptibility and/or red blood cell invasion. The Laboratory of Viral Diseases (LVD) is active with Cambridge University in studies using vaccinia virus recombinants to express genes of respiratory viruses and with the Institute of Virology (Glasgow) on the mechanisms of viral DNA replication.

U.S.S.R.: The involvement of NIAID in the U.S.-U.S.S.R. Agreement for Cooperation in the Fields of Medical Science and Public Health has been limited to the program areas of Influenza, Acute Respiratory Diseases, and Viral Hepatitis, in which the CDC is the lead Public Health Service agency. Several NIAID awardees in influenza have participated in these bilateral activities. In recent years, LID/NIAID involvement in the viral hepatitis area has shifted from hepatitis B virus to non-A, non-B hepatitis in the Soviet Union. LID/NIAID is now collaborating with the Ivanovsky Institute of Virology (Moscow) to investigate outbreaks of enterically transmitted non-A, non-B hepatitis in the U.S.S.R. Viral particles have been visualized in specimens from the Soviet Union that resemble in size and surface structure those from Algeria, India, and Pakistan. In November 1986, two virologists from the Ivanovsky Institute visited LID/NIAID and LIR/NIAID to exchange specimens and information on viral diseases and to participate in a workshop on non-A, non-B hepatitis. There was one Soviet Visiting Scientist at NIAID in FY 1987.

Venezuela: In FY 1987, one Venezuelan Visiting Scientist was resident in the NIAID intramural program. LID/NIAID, the National Institute of Dermatology (Caracas), the J.M. de los Rios Children's Hospital, and the Miguel Perez Hospital have collaborated to test rotavirus vaccine candidates in Venezuelan children. Infants 1–10 months of age received a single oral dose of rhesus rotavirus vaccine (serotype 3) or a placebo and were followed weekly for 1 year. Only 5 of 28 rotavirus diarrhea episodes occurred in vaccinated infants, for an overall vaccine efficacy rate of 68 percent. Side effects were minor and infrequent. Vaccine failures were caused by serotypes other than type 3. It therefore appears that the rotavirus vaccine protection is serotype-specific.

Yemen: In FY 1987, NIAID staff visited the Yemen Arab Republic (North Yemen) to explore the possibility of involvement by the NIAID-AID Regional Project in AID/Sanaa's malaria control project.

Zaire: LIR/NIAID cooperates with CDC, IMT/Antwerp, and the Ministry of Health of Zaire in Project SIDA, which conducts multidisciplinary studies of AIDS in that country.

Taiwan: U.S. and Taiwanese scientists carry out collaborative research activities under the NIH-Taiwan Cooperative Agreement. The American Institute in Taipei, which acts on behalf of the Department of State, works in association with the NIH in administering the program; the Coordination Council for

North American Affairs in Washington, D.C., acts on behalf of the National Science Council of Taiwan. During FY 1987, there was one active project among the University of Hawaii, National Taiwan University, and the University of Korea to investigate Hantaan virus infection in Taiwan. Stratified surveys have been conducted in 20 townships in five geographic areas. Prevalence of seropositivity ranged from 7.7 percent in Orchid Island aborigines to very low levels in Hakka Chinese in Man Chow. Hantaan virus seropositivity in rats was 21.4 percent at Orchid Island and 7.7 percent overall. Patients with renal disease did not have higher Hantaan virus titers than the general population. The infectious disease program area has been expanded in FY 1987 to include parasitic diseases. NIAID is reviewing new preproposals in schistosomiasis, malaria, filariasis, *Angiostrongylus cantonensis,* and AIDS.

Intramurally, LID/NIAID and the University of Washington Medical Research Unit (Taipei) are collaborating on hepatitis delta virus studies.

Activities With International and Multinational Organizations

Agency for International Development: In December 1981, NIAID entered into an agreement with the U.S. Agency for International Development to manage a 5-year, $7.0 million project on the epidemiology and control of vector-borne diseases in the Near East. AID has recently agreed to extend the NIAID-AID Regional Project for 5 more years with an additional $5.0 million. AID identified the following disease priorities in health: acute respiratory infections, including tuberculosis; diarrheal diseases; parasitic diseases; and tropical viruses (e.g., arboviruses, hepatitis). In FY 1987, AIDS was added to this list of health priorities. NIAID and AID are involved in several cost-sharing activities such as the development and evaluation of new and improved vaccines and malaria immunity and vaccine development.

During FY 1987, NIAID also joined with the Walter Reed Army Institute of Research, CDC, and AID to commission an external evaluation by the Board on Science and Technology for International Development (BOSTID) and the Institute of Medicine of the National Academy of Sciences on the "U.S. Capacity to Address Tropical Infectious Disease Problems," which was published in 1987. In FY 1987, the NIAID-sponsored Institute of Medicine *Report on International Priorities for Vaccine Development* appeared in print. NIAID and AID are using both documents in their program evaluation and planning processes.

AID'S renewed programmatic interest in applied research also has resulted in the development of eight new or expanded applied research programs. NIAID awardees and staff and foreign institutions participate in and/or seek funding from these new initiatives. They are:

- Expansion of the AID Program in Science and Technology Cooperation to include special emphasis areas in Biotechnology, Immunology, and the Biologic Control of Vectors;
- Expansion of the AID-funded BOSTID Research Grants Program to include new program areas in Mosquito Vector Field Studies, Rapid Epidemiologic Assessment Methods, and Acute Respiratory Infection in Children;
- A new Diarrheal Disease Research Grants Program administered by the Harvard International Development Corporation;
- A new Diagnostic Technology for Community Health Grants Program administered by the Program for Appropriate Technology in Health, Inc.;
- A new Research Grant Program for Historically Black Colleges and Universities administered by the International Science and Technology Institute, Inc.;
- A new Vector Biology and Control Grants Program administered by the American Institute of Biological Sciences, Inc.;
- A new AIDS Technical Assistance Program administered by Family Health International, Inc., of Research Triangle Park, North Carolina; and
- A new AIDS Communication Program administered by the Academy for Educational Development.

World Health Organization: During FY 1987, NIAID cooperation with the World Health Organization continued to expand, particularly following the establishment of the new WHO Special Program for the Prevention and Control of AIDS (SPA). Significant activities in FY 1987 included:

- Co-sponsorship of the workshop on AIDS in Africa at the WHO Regional Office for Africa in Brazzaville in November 1986;
- Designation of the NIAID Director as the principal contact person for the WHO Collaborating Center on AIDS, established at NIH in 1987;
- Co-sponsorship of the Third International Conference on AIDS held in Washington, D.C., in June 1987;
- Award of an NIAID research contract to the Pan American Health Organization, the Regional Of-

fice of WHO for the Americas to study HIV infection and AIDS in Latin America and the Caribbean; and

- Participation of NIAID staff and awardees in SPA/WHO-convened informal consultations and meetings.

In addition to the recent designation of the NIH as a WHO Collaborating Center on AIDS, NIAID is the host of two other WHO Collaborating Centers: the WHO Collaborating Center for Allergic Diseases, established in 1985, and the WHO Collaborating Center for Research in Microbial Vectors, initiated in 1987. NIAID also provides indirect support to U.S. institutions that serve as WHO Collaborating Centers. Among the most active are WHO Collaborating Centers in Arboviruses at Yale, Enteroviruses at the Baylor College of Medicine, Influenza at the St. Jude Children's Research Center, and Immunology at the Scripps Clinic.

Extramural Programs

The major portion of NIAID's financial resources are used by the extramural programs, which manage grants, collaborative agreements, and contracts that are awarded competitively to academic and research institutions. In FY 1987, the Microbiology and Infectious Diseases Program, the Immunology, Allergic and Immunologic Diseases Program, and the new Acquired Immunodeficiency Program are the three extramural programs that support research and research training awards. The Extramural Activities Program is responsible for grants and contract management, research manpower development, the organization as well as the conduct of Institute-convened peer review groups, and executive secretariat support to the National Advisory Allergy and Infectious Diseases Council (NAAIDC). The extramural program now has responsibility for initial review to institutes for investigator-initiated grant applications in response to announcements, the AIDS emergency, and the expansion of NAAIDC to include AIDS.

Four extramural award mechanisms provide flexibility in the exchange and cooperation between U.S. scientists and counterparts in developing countries. They are:

- The International Collaboration in Infectious Diseases Research Program;
- The Tropical Diseases Research Unit (TRU) Program;
- The International Tropical Diseases Research Fellowships; and
- The Senior International Fellowship (SIF), with an emphasis on tropical diseases.

The ICIDR Program, which emphasizes the peer relationship between U.S. institutions and their foreign counterparts, requires that 70 percent or more of the award be spent overseas and that all research be approved in advance by the appropriate national authorities. The ICIDR Program focuses on infectious diseases, is limited to developing countries, and is managed through the research grant rather than the contract award mechanism. The ICIDR Program has now been through two award cycles and competitive renewal for the incumbents and new applicants is now under way, with funding expected in mid-1988 (See Table VII–1).

The TRU Program, established in 1978, is intended to expand U.S. institutional research capability in infectious diseases of importance in the tropics and to developing countries. The TRU Program provides program project (PO-1) awards to domestic research institutions for multidisciplinary research in tropical medicine. It also provides opportunities for research training in tropical diseases for young U.S. and foreign scientists. In contrast to the ICIDR Program, 70 percent or more of the TRU award must be spent in the United States. Recompetition of the 5-year, renewable TRU awards took place in 1985 (see Table VII–2).

The ITDR Fellowships are a variant of the FIC International Research Fellowships initiated by NIAID in 1979. NIAID has funded a limited number of ITDR fellowships for midcareer scientists from developing countries to come to a U.S. institution to conduct collaborative research relevant to tropical disease problems. The SIF fellowship, with an emphasis on tropical diseases, is a complementary program for midcareer to senior U.S. scientists who wish to spend a sabbatical period conducting collaborative research on a tropical medicine problem in a developing country. No ITDR or SIF/tropical medicine awards were made in FY 1987 because of severely limited domestic research training and career development funds. ITDR or SIF/tropical medicine awards will be considered by NIAID on a case-by-case basis, provided that domestic research training or career development programs will not be adversely affected.

In FY 1987, NIAID initiated the International Collaboration in AIDS Research (ICAR) applications, which were due in September 1987 and will be awarded in mid-1988. The ICAR Program is similar to the ICIDR Program in that only U.S. applicants are eligible to apply, the PO-1 mechanism will be employed, and at least 70 percent of the award must be spent outside the United States. The ICAR Pro-

Table VII–1

ICIDR PROGRAM AWARDS, FY 1987

Institution	Site	Research Area
Program Project (P0-1) Awards		
Harvard University	Brazil (FIOCRUZ)	Leishmaniasis, malaria, Chagas' disease; focus on molecular biology and immunology
Cornell University (University of Bahia)	Brazil	Cutaneous and visceral leishmaniasis, Chagas' disease; focus on epidemiology, genetics, and immunopathology
Michigan State University	Sudan (University of Khartoum) (Ministry of Health)	Malaria, schistosomiasis, onchocerciasis, leishmaniasis; focus on pharmacology and immunology
Tulane University	Colombia (COLCIENCIAS)	Chagas' disease, filariasis, onchocerciasis, leishmaniasis
Johns Hopkins University University of Maryland	Peru (Peruvian University Cayetano Heredia)	Bacterial diarrhea; focus on shigellosis, typhoid fever, and salmonellosis
Wayne State University	Ethiopia (Armauer Hansen Research Institute)	Leprosy and leishmaniasis; focus on immunology
Exploratory Grants		
Harvard University	Indonesia (LITBANKES)	Filariasis; focus on epidemiology
Albert Einstein College of Medicine	Venezuela (CEPIALET)	Leprosy; focus on immunology

gram differs in that the foreign counterpart need not be a developing country.

International Conferences, Seminars, and Meetings

During FY 1987, NIAID organized, funded, and/or actively participated in a variety of sessions relevant to international research. The most important are summarized in Table VII–3.

Intramural Programs and Activities

NIAID intramural research is carried out by approximately 600 staff members in 14 laboratories, 11 located in Bethesda and 3 Rocky Mountain facilities in Hamilton, Montana. Although nearly 80 percent of NIAID staff are in the intramural laboratories they constitute only about 20 percent of the NIAID budget.

Several sections of the Bethesda-based laboratories are physically based at the Cancer Research Facility in nearby Frederick, Maryland, which houses maximal-containment laboratories and NIAID/NIH contract support services. NIAID also has intramural contracts in the metropolitan area for support of nonhuman primate, hepatitis, and AIDS research. During FY 1987, one LIR/NIAID staff member was permanently assigned in charge of laboratory operations for Project SIDA in Kinshasa, Zaire.

The NIAID Laboratory of Parasitic Diseases is the largest research facility in the United States totally committed to biomedical research on human parasitic diseases. The Office of the Scientific Director of NIAID and the Laboratory of Pathobiology are responsible for tick and vector-borne disease research. The Laboratory of Infectious Diseases is heavily involved in international studies on respiratory viruses, viral diarrheal agents, and infectious hepatitis. LIR/NIAID also has recently developed a significant research effort in the molecular biology of dengue viruses. The Laboratory of Immunoregulation is responsible for Project SIDA in Zaire and the bulk of NIAID intramural AIDS research. The Laboratories of Molecular Microbiology, Viral Diseases, Immunopathology, Persistent Viral Diseases,

Table VII–2

TROPICAL DISEASE RESEARCH UNIT AWARDS, FY 1987

Institution	Research Area
Robert Breck Brigham Hospital, Harvard University	Immunology of Four Parasitic Diseases of Man (Filariasis, Leishmaniasis, Malaria, and Trypanosomiasis)
Case Western Reserve University	Tropical Disease Research Unit (Schistosomiasis, Filariasis, Clinical Immunology)
New York University	Immunology of Malaria

Table VII–3

NIAID INTERNATIONAL CONFERENCES, SEMINARS, AND MEETINGS, FY 1987

Date	Meeting	Location
September–October 1986	International Conference on Antibiotics and Anti-Infective Chemotherapy (ICAAC)	New Orleans, LA
October 1986	International Conference on Food Allergy	Taramino, Italy
October 1986	Infectious Disease Society of America Meeting	New Orleans, LA
October 1986	10th Seminar on Amebiasis	Mexico City
October 1986	International Symposium on Epstein-Barr Virus	St. Petersburg, FL
November 1986	International Symposium on Research Toward Rabies Prevention	Washington, DC
November 1986	AFRO/WHO Conference on AIDS in Africa	Brazzaville, Congo
November 1986	Workshop on Non-A, Non-B Hepatitis	Bethesda, MD
December 1986	Workshop on Malaria in Africa	Washington, DC
December 1986	35th Annual Meeting of the American Society of Tropical Medicine and Hygiene	Denver, CO
December 1986	Pan American Congress of Infectious Diseases	San Juan, PR
March 1987	U.S.-Japan Hepatitis Panel Meeting	Otsu City, Japan
May 1986	Workshop on AIDS in Africa	Bethesda, MD
June 1987	Third International Conference on AIDS	Washington, DC
July 1987	International Symposium on Verocytoxin-Producing Infections	Toronto, Canada
July 1987	U.S.-Japan Joint Leprosy and Tuberculosis Conference	Bethesda, MD
July 1987	U.S.-Japan Joint Committee of the Medical Sciences Program Meeting	Bethesda, MD
July 1987	International Workshop on *Campylobacter Pyloridis*	Keystone, CO
July 1987	Seventh International Congress of Virology	Ottawa, Canada
August 1987	U.S.-Japan Parasitic Diseases Conference	Williamsburg, VA
September 1987	Third International Conference on Malaria and Babesiosis	Annecy, France

and Infectious Diseases, however, have one or more research projects in AIDS.

NIAID intramural laboratories also benefit considerably from the participation of foreign scientists who spend periods of one to several years at the NIH for research training or participate as mature scientists in the NIAID research effort. The host laboratory pays for the stipends, insurance, and dependents' allowance of participants in the Visiting Program. Visiting Fellows are young foreign scientists within 3 years of their doctoral degree. They receive the same benefits as a U.S. citizen but do not occupy a full-time equivalent position. Visiting Associates and Visiting Scientists are, respectively, midcareer and established foreign investigators at the NIH for a time-limited period. These more senior scientists do occupy one of NIAID's full-time equivalent positions, and their salary is commensurate with their training and experience. In addition to Visiting Scientists, NIAID provides laboratory space and resources to a number of Guest Researchers whose stipends are paid from external sources (e.g., WHO, AID, national government, home institution).

During FY 1987, NIAID provided support for a total of 120 foreign scientists as Visiting Fellows (75), Associates (27), and Scientists (18) from 29 countries. The largest number were from Japan (18); India (15); United Kingdom (9); France (8); Australia (7); Canada, China, and Italy (6); Spain (5); Argentina and the Federal Republic of Germany (4); and Belgium, Brazil, and Israel (3). There were two Visiting Scientists from Korea, Netherlands, Poland, and Switzerland. Countries with one participant in the Visiting Program in FY 1987 were Chile, Denmark, Guyana, Hong Kong, Ireland, Norway, Peru, Tunisia, U.S.S.R., and Venezuela.

Chapter VIII
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Introduction

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) conducts and supports research on many of the most debilitating diseases that affect the public health. The Institute supports basic and clinical research on numerous important diseases, including the many forms of arthritis, diseases of the musculoskeletal system, and diseases of the skin, as well as on the normal structure and function of joints, muscles, bones, and skin. Basic research involves a wide variety of disciplines, including immunology, genetics, molecular biology, biochemistry, virology, and pharmacology. Congress and the President recognized the importance of these research areas with the enactment of P.L. 99-158, a major provision of which directed the establishment of a separate institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

NIAMS is involved in a wide range of international activities. The Institute is particularly pleased by the renewed and increased activity in the U.S.-U.S.S.R. Cooperative Program in Arthritis. In 1987 great progress was reported in two areas of research, Lyme borreliosis and juvenile arthritis. Most significantly, a plan was developed to continue collaborative studies during 1987–89, and a new area, epidemiology of rheumatic diseases, was added. These areas of collaboration were included in the Bilateral Health Agreement signed in April 1987.

Highlights of Recent Scientific Advances Resulting From International Activities

FY 1987 collaborative activities produced several noteworthy findings in the Institute's areas of study.

American and Brazilian researchers recently established that in Brazil, endemic pemphigus foliaceus seems to be the same disease as the sporadic form found throughout the world.

In England, researchers have developed unique capabilities to synthesize structures like those in cartilage with configurations that confer different properties, including variations in weight-bearing ability.

Finally, according to a study conducted in Canada, rheumatoid arthritis is associated with a major decrease in survival.

Summary of International Programs and Activities

Country-to-Country Activities and Other Bilateral Agreements

Federal Republic of Germany: A delegation from the Federal Republic of Germany (FRG) met at the NIH May 15, 1987, to learn about multipurpose arthritis centers in the United States in order to explore the possibility of establishing them in the FRG. The delegation visited centers in Birmingham and Boston. The Director, NIAMS, met with the German visitors again in June to review the report on the German Rheumatism Research Centre in Berlin.

Italy: During 1987, NIAMS began discussions with Italian researchers at the Instituto di Medicina Interna at the University of Padua to explore opportunities for collaborative research projects. Important areas of mutual interest to both institutes include the epidemiology of osteoporosis and its treatment. As a result of these discussions, a new area of cooperation, musculoskeletal diseases, will be added to the U.S.-Italy science and technology bilateral agreement, and the development of specific collaborative studies is being pursued.

U.S.S.R.: The U.S.-U.S.S.R. Cooperative Program of Arthritis generated considerable interchange in 1987. Most significantly, a plan was developed for 1987–89 that will ensure that the program remains active. The agreement was signed on January 24, 1987, and included in the bilateral health agreement signed in April 1987.

Progress has been achieved in two areas of joint investigation, Lyme borreliosis and juvenile arthritis.

Lyme borreliosis: A Soviet investigator participated in the third International Conference on Lyme Disease and Related Disorders, held in New York in September 1987. The conference was co-sponsored by the New York Academy of Sciences and the New York State Department of Health. Following the conference, he worked with an Institute researcher in Boston to perfect culturing techniques, antigen preparation, and serologic testings methods. A manuscript in preparation will describe the clinical and serologic findings of Soviet patients with tick-borne erythema (Lyme borreliosis) and compare them to patients with Lyme borreliosis in the United States.

Juvenile arthritis: Two noteworthy collaborative U.S.-U.S.S.R. projects in juvenile arthritis took place during FY 1987, and a third is planned. The results of a randomized trial comparing D-penicillamine, hydroxychloroquine, and placebo have been published in the United States, (*New England Journal of Medicine*, May 1986) and in the U.S.S.R. (*Vopr. Rheum.*, 1987). Joint X-rays, taken during this study to determine the effects of drugs on bone and cartilage deterioration or healing, are being evaluated.

Also during FY 1987, a cooperative study comparing treatment of juvenile arthritis with auranofin versus placebo was completed and is being analyzed. It is anticipated that the results of this study will be presented at the American Rheumatism Association meeting in May 1988.

A double-blind, randomized study of methotrexate versus placebo in juvenile arthritis will be conducted. The United States will provide the protocol, study drugs, and study data booklets. Initiation of the study in the U.S.S.R. is pending approval by a Soviet pharmacy committee.

NIAMS began exploring opportunities for epidemiologic studies of rheumatic diseases in Eskimos and American Indians of the northwest United States in collaboration with the Centers for Disease Control and the Indian Health Service. These studies will lay the groundwork for future collaboration with the U.S.S.R. through comparison with comparable studies of rheumatic diseases in northeastern Siberian Indians and other relevant populations in the U.S.S.R.

Activities With International and Multinational Organizations

The NIAMS Director, who serves as President of the Pan American League Against Rheumatism, delivered the keynote address of the ninth Pan American Congress in Buenos Aires, Argentina, in November 1986. In addition, he was made an honorary member of the British Society of Rheumatology.

The Scientific Director of NIAMS serves as Secretary-General of the International Union of Immunological Societies. In August 1987, he participated in the union's council meeting in Zagreb, Yugoslavia.

Extramural Programs

American researchers, working in conjunction with Brazilian investigators, have recently established that the endemic form of pemphigus foliaceus found in Brazil is immunologically identical to the sporadic form found throughout the world. Of the 150 patients with the endemic form who were examined, all demonstrated autoantibodies identical to those seen in the sporadic cases in the United States. Testing the antibodies for their biologic function in animal models of pemphigus has also demonstrated actions of the antibodies that are essentially identical in both patients with the endemic form of the disease and patients with the sporadic form. This finding suggests that endemic pemphigus foliaceus and sporadic pemphigus foliaceus are the same disease.

Researchers at the Kennedy Institute of Rheumatology, London, England, have developed unique capabilities to synthesize proteoglycan structures (such as those in cartilage) with varying configurations. In collaboration with scientists at Columbia University, the London scientists have determined the physical properties of these special biochemical compounds. For example, a high degree of aggregation—attachment of additional side chains—was shown to immobilize proteoglycans, giving them stronger load-bearing properties.

Rheumatoid arthritis is associated with a major decrease in survival, according to a prospective, longitudinal study conducted at a referral center in northern Saskatchewan Province over a 12-year period. Researchers from the Department of Medicine, University of Saskatchewan, Saskatoon, Canada, and the Department of Medicine, Stanford University School of Medicine, California, determined that survival rates for rheumatoid arthritis patients were approximately 50 percent lower than those in the general population matched for age and sex. The decrease

in survival began early in the disease and increased throughout its course. This study was a subproject of the NIAMS-supported American Rheumatism Association Management Information System grant.

Support continued for an investigator at the Weizmann Institute of Science, Rehovot, Israel. This investigator has had unique and extensive experience in the use of autoantigen-specific T-cell lines as a means of understanding the pathology of and developing new therapies for a variety of autoimmune diseases. Using long-term lines and clones of T lymphocytes, he studies the pathogenesis and manipulation of adjuvant arthritis in an animal model.

The Muscle Biology Program supports two international projects. One, in Mexico City, Mexico, is studying the functional role in muscle excitation of calcium flow controlled by the voltage difference between the inside and outside of the cell. The scientists are simultaneously monitoring the ionic currents, movement of charge, and transients of calcium concentration. This group has isolated a calcium ion channel in which calcium flow occurs on the same time course as tension development in muscle twitch.

The second project involves researchers at the University of Miami, Florida; Oxford University, United Kingdom; and the European Molecular Biology Laboratory (EMBL) synchrotron radiation source (DESY), Hamburg, FRG. This is a multidisciplinary study of the interaction of calcium ions with the regulatory proteins of muscle and subsequent changes in the way the proteins interact. Current experiments indicate that Troponin-C, the calcium-binding regulatory protein, can be labeled with a fluorescent indicator, then injected into intact muscle fibers. This provides a way to measure bound calcium, which can be correlated with the development of force. Additional studies are directed at the processes and structural changes that occur during the development of tension.

Two fellowships supported through the Muscle Biology Program have international components. At the Weizmann Institute in Israel, one Fellow is learning molecular genetic techniques relevant to muscle development with the goal of understanding the mechanisms that coordinate the synchronous expression of sarcomere proteins. This researcher has shown that coordination is brought about by binding of a common regulatory factor.

A second Fellow is spending 2 months at the EMBO Laboratory in Heidelberg, FRG, to be trained in preparation and electron microscopy of freeze-hydrated specimens of skeletal muscle. This technique is being pioneered in Europe.

International Conferences, Seminars, and Meetings

During FY 1987, the Director, NIAMS, took part in the following activities:

- Lectured at the 22nd Congress of the German Society of Rheumatology in Freiburg;
- Chaired a seminar entitled "Research Opportunities in Rheumatology for the Americas," sponsored by the Pan American League Against Rheumatism, in Rio de Janeiro, Brazil; and
- Chaired a session on Sjogren's syndrome and scleroderma at the 11th European Congress of Rheumatology, in Athens, Greece.

In April 1987, NIAMS sponsored a scientific conference on Kashin-Beck disease, a form of osteoarthritis, in Bethesda, Maryland. The conference included a video film of Kashin-Beck disease in China, supplied by a professor of orthopaedic surgery at Xian Medical University in China. More than 2 million Chinese are estimated to be afflicted with the disease, which occurs in children and young adults in the hilly, agricultural regions of Northern China, the Eastern Republic of the U.S.S.R., and Korea. A senior consultant for UNICEF in China, who spoke at the conference, stated that the study of Kashin-Beck disease is a major research program in China. It is thought that studies of this disease may provide insights into the cause of osteoarthritis, the most common form of arthritis in the United States, which affects some 16 million Americans.

NIAMS also co-sponsored a workshop on research directions in osteoporosis, held at the NIH in February 1987. More than 750 physicians and scientists, including approximately 50 participants from Canada, England, and Asia, attended the workshop, and three foreign speakers made presentations. The workshop provided a scientific update on current knowledge and research relating to osteoporosis, and specific recommendations for future research efforts were developed.

At the scientific meeting of the International Society for the Assessment of Technology in Health Care, held in Rotterdam, Netherlands, in May 1987, the Associate Director for Prevention, Epidemiology, and Clinical Applications presented a paper on NIH planning for clinical trials for assessing health care technologies.

In November 1986, the NIAMS Epidemiology/Data Systems Program Officer participated in a workshop entitled "Epidemiologic Studies in Latin America." The workshop was part of the Ninth Pan American Congress of Rheumatology, held in Buenos Aires, Argentina. It included presentations and critiques of

multinational studies of osteoporosis and systemic lupus erythematosus.

The Muscle Biology Program provided partial support for three conferences of international consequence. One was the International Congress of Biophysics, in Jerusalem, Israel. The Director of the Muscle Biology Program attended this conference, which included sessions on the biophysics of connective tissue, muscle membranes, and muscle proteins.

The Gordon Research Conference on Contractile Proteins in Muscle, held in July 1987, featured a large number of speakers from Europe and Japan. The informal nature of this conference provided an opportunity for U.S. researchers who are conducting skeletal muscle studies to interact directly with foreign investigators who have overlapping research interests and different expertise.

The Muscle Biology Program also provided support for several U.S. scientists to attend and present papers at the Fernstrom Symposium on the Neuromuscular Junction. This conference, held in Sweden, focused on aspects of excitation-contraction coupling, including studies on:

- Structure and function of ion channels;
- Acetylcholine release and reception;
- Degenerative mechanisms; and
- Genetic expression in muscle.

The proceedings of this symposium will be published.

Two intramural scientists were invited lecturers at the scientific meeting of the European League Against Rheumatism in Athens, Greece, in July 1987. One gave the opening plenary lecture, entitled, "Where Do Autoantibodies Come From?"

An intramural researcher from NIAMS was an invited lecturer at the annual meeting on inflammation sponsored by Birmingham University at Birmingham, United Kingdom. The Chief of the Laboratory of Physical Biology and one of his senior scientists also were invited lecturers and session organizers at a meeting entitled "Crossbridges and Muscle Contraction," which was sponsored by Teikyo University School of Medicine and was held in Hakone, Japan, in October 1986.

Intramural Programs and Activities

A researcher from the Department of Physics and Biophysics, Massey University, New Zealand, visited NIAMS in 1987 to complete work on the molecular structures of fibrous proteins. He had worked at the Institute as a Visiting Scientist 2 years previously, and the visit in 1987 continued the collaboration he has had with an intramural researcher from NIAMS since that time. As a result of this visit, two research papers were completed.

During FY 1987, a researcher from NIAMS hosted a scientist from the Department of Microbiology, Hadassah University Medical School, Jerusalem, Israel. The research in Israel centers on the structural properties of surface layers of proteins or glycoproteins that form the outermost coverings of many kinds of bacteria and other micro-organisms. The purpose of this collaborative visit was to investigate the incidence of such layers in various pathogenic and nonpathogenic strains of *Bordetella pertussis*. The initial phase of this work is to characterize by electron microscopy and image processing a periodic layer detected in Tohama III, a nonpathogenic strain, to identify the molecule or molecules involved and to relate this information to the possible incidence of this and other related proteins in other strains of *B. pertussis*.

Two researchers from the Federal Republic of Germany, one from the University of Tubingen and one from the EMBO Laboratory, Hamburg, hosted an intramural scientist at DESY, Hamburg, for 2 weeks in April 1987. The visit allowed the intramural scientist to use high-intensity sources of X-rays to study the structure of actively contracting muscle. One of the FRG scientists visited the NIH subsequently to use a fine-focus camera to study the structure of crossbridges in myosin.

An intramural scientist collaborated with two scientists at the EMBO Laboratory, Heidelberg, FRG, to learn cryoelectronmicroscope techniques for studying the structure of muscle fibers at high resolution with fixation.

The Section on Chemical Immunology of the Arthritis and Rheumatism Branch reported progress from three international researchers working in the Section in 1987:

- A Visiting Scientist from Belgium was able to make significant advances in isolation of the genes that code for the receptor for IgE on mast cells.
- A Visiting Fellow from the United Kingdom developed significant new information on the possible role of protein kinase C in the triggering function of the receptor for IgE on mast cells.
- A Visiting Fellow from Argentina was able to demonstrate calcium ion-independent stimulation of phosphotidyl inositol hydrolysis, a finding that substantially clarified certain discrepant observa-

tions related to activation of mast cells by the receptor for IgE.

An intramural scientist collaborated with the Chief of Rheumatology at the University of Vienna Hospital, Austria, on the relationship between certain transplantation antigens (class II) and specific autoantibodies in patients with systemic lupus erythematosus. The correlation found may help to identify a distinct subset of these patients.

In FY 1987, the NIAMS intramural research program hosted four Visiting Fellows (two from Japan and one each from Italy and United Kingdom); three Visiting Scientists (one each from Belgium, Japan, and United Kingdom); and one Visiting Associate (from India).

Chapter IX
National Institute of Child Health and Human Development

Introduction

The National Institute of Child Health and Human Development (NICHD) conducts and supports research on the reproductive, developmental, and behavioral processes that determine the health of children, adults, families, and populations. In pursuit of this mission, NICHD administers a multidisciplinary program of research and research training in this country and overseas.

The Institute's programs are based on the concepts that adult health and well-being are determined in part by episodes early in life, that human development continues throughout life, and that reproductive processes and the management of fertility are of major concern not only to the individual but to the whole of society. The Institute supports research in the reproductive sciences to develop knowledge that will enable men and women to regulate their fertility with methods that are safe, effective, and acceptable to various population groups, and to overcome problems of infertility. In the population, social, and behavioral sciences, the purpose of Institute-sponsored research is to understand the causes and consequences of population change.

Research for mothers, children, and families is designed to:

- Advance knowledge about fetal development, pregnancy, and birth;
- Identify the prerequisites of optimal growth through infancy, childhood, and adolescence;
- Contribute to the prevention and treatment of mental retardation; and
- Advance knowledge about and prevent childhood injuries and accidents.

Highlights of Recent Scientific Advances Resulting From International Activities

Down Syndrome

Down syndrome is the most common genetic birth defect associated with mental retardation. It results from the presence of an extra copy of a small portion of chromosome 21. An investigator from Israel is exploring, at the molecular level, the mechanisms whereby this portion of the chromosome produces Down syndrome. The genes residing at that region will be cloned and characterized, their structure and organization will be analyzed, and polymorphic markers within them will be identified by detailed mapping. The expression of each isolated gene will be examined in trisomy 21 cells and in fetal tissue to determine the dosage effect. The influence exerted on development and morphogenesis by overexpression of a specific gene will be studied by transferring the gene of interest into mouse embryos to produce transgenic mice that overexpress this gene. The information obtained in this study should permit definition of the biochemical pathways that are affected in Down syndrome and may pave the way for the development of therapies to ameliorate or prevent some of the symptoms of this condition.

NICHD also is supporting a study that will test the hypothesis that a genetic predisposition to trisomy 21 is associated with DNA sequences on certain chromosome 21s. Using 20 Greek families that have a child with trisomy 21 and at least one normal child, the investigators compared four DNA restriction fragment length polymorphisms of these families with a control population of 27 Greek families seen for prenatal diagnosis of hemoglobinopathies. Preliminary data suggest that one particular chromosome

21 marked with a certain haplotype for the polymorphic sites examined is found more frequently in the chromosome 21s that were involved in nondisjunction. The investigators hypothesize that some fraction of this particular chromosome 21 in Greeks contains DNA sequences that have a tendency to nondisjunction, leading to trisomy 21. This preliminary observation will be expanded by examination of more Greek and Japanese families that have trisomy 21 children.

Multinational Comparison of Perinatal Mortality Rates

A study with Australia, Japan, Norway, and United Kingdom (Scotland) and five participating States (Michigan, Missouri, New York, North Carolina, and Utah) is being conducted to develop up-to-date information to compare and analyze the U.S. perinatal and infant mortality rate with that of other developed countries in recent years (1980–84). The focus of the project has been on multilateral comparisons between the United States and other national groups, such as Scandinavians or Japanese, who have achieved the lowest perinatal or infant mortality rates in the world in recent years.

The higher perinatal mortality rate in the United States may be the result of an excess number of low birth weight infants born in this country. However, at any given birth weight (<2,500 g), the United States has nearly the lowest birth weight-specific perinatal mortality rate in the world. Although this favorable comparison could result from our technology-intensive approach to neonatal care, alternative explanations deserve attention. Because it is known that preterm babies are at a higher perinatal mortality risk than babies of equal weight who are born at term, one objective of these comparisons is to distinguish the mortality rates associated with two types of low birth weight infant: preterm births and small-for-gestational-age (SGA) births. Also, it is likely that a higher proportion of low birth weight infants in the United States is in the SGA category, which could account for the favorable perinatal mortality rates found among low birth weight infants in this country, or it may be that the U.S. cumulative birth weight distribution is shifted toward smaller deliveries, which then "improves" the low birth weight-specific perinatal mortality rate for the U.S. compared to that of other countries. In view of the expense associated with high-technology neonatal care, it is important to ensure fair comparisons by adjusting for different inherent risks in the infant populations involved.

Metabolic Effects of Oral Contraceptives

As part of an NICHD-supported project, a metabolic laboratory in England is quantifying the differential metabolic effects induced by various brands and doses of oral contraceptives (OCs). Oral glucose tolerance tests with insulin and lipid protein assays are being conducted in users of nearly 10 brands of OCs. Comparisons of glucose and lipid metabolic effects made among brands containing the same progestins will offer insight into dose-related effects. Metabolic comparisons made between brands containing the similar doses of different progestins will yield data on potency differences. This research will provide for state-of-the-art lipid determinations that are known predictors of future heart disease.

Placental Hormones and Intrauterine Growth Retardation

This research project, being conducted in Canada, studies the role of pituitary peptides in fetal development. This research is designed to enhance understanding of normal mechanisms and pathologic variation in human fetal development. One study is examining the role of pituitary peptide in altering adrenal synthesis of corticosteroids. Newly isolated peptides of this type are being tested to determine whether they act alone or together with ACTH (adrenocorticotropic hormone) in stimulating cortisol synthesis. A second study is devoted to the ontogeny of these peptides and the search for other peptides that may be involved in fetal adrenal growth and steroidogenesis. Yet another subproject is examining the effect of peptides on adrenal steroid synthesis and growth.

This project is enhancing knowledge of the fetal adrenal and its maturation as well as its role in the initiation of labor, a major factor in the prevention of prematurity.

Role of Placenta in Prematurity

This research project, being conducted in Canada, is devoted to the study of action of placental and pituitary hormones, particularly prolactin and placental lactogen (ovine type). There are five major areas of focus:

- Human studies of prolactin and growth hormones that examine and define clinical problems of prolactin secretion and animal studies to examine neuroendocrine factors that influence the secretion of prolactin and pituitary hormones;
- Studies of the receptors for prolactin and growth hormone;

- Studies to investigate the molecular biology of prolactin and growth hormone receptors in tissue culture;
- Studies to purify and characterize rat placental lactogen, a hormone of interest because investigators have noted that ovine placental lactogen binds to human growth hormone receptor, and this hormone may be useful in treating growth hormone-deficient dwarfs; and
- Studies to identify, purify, and characterize human brain and pituitary growth factors, intended to enhance knowledge of the role of the placenta in regulating growth and development and its relationship to intrauterine growth retardation.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

Argentina: NICHD is collaborating with the Centro Rosarino de Estudios Perinatales, Rosario, Argentina, in a randomized controlled clinical trial of calcium supplementation during pregnancy for the prevention of preeclampsia. Staff visits have been conducted in both countries, and the project will continue during 1988.

China: Scientific information, experimental reagents, antisera, standards, and radioimmunoassay kits have been exchanged with Chinese scientists as a result of discussions and visits to China under the U.S.-China Health Protocol of the Agreement on Science and Technology. These activities have been concerned specifically with research in reproductive biology and contraception. In October 1986, NICHD staff participated in a symposium on gossypol in Wuhan, China. An NICHD staff member gave a presentation on some of the gossypol analogues that NICHD has tested for toxic effects in its contract facilities. The NICHD staff then visited The Third Affiliated Hospital, Beijing Medical College, and gave several lectures. Topics included research on sex differentiation, microsurgery, new methods in the delivery of contraceptives, new developments in obstetrics and gynecology, and magnetic resonance imaging.

Finland: The U.S.-Finland Collaborative Study is examining the effect of maternal Vitamin E folate and Vitamin B-12 status on the risk of producing a child with a neural tube defect. Using the national birth defects registry, children with birth defects are identified. Prenatal history is collected from the registry and maternal medical records. Blood collected from each mother and a suitable control mother early in pregnancy is then assayed for folate and Vitamin B-12 to determine whether or not neural tube defects are associated with deficiencies of these vitamins. To date, a protocol has been developed and data-gathering instruments have been designed. Affected children are now being identified.

Guatemala: NICHD is collaborating with Guatemalan investigators on the analysis of a prospective followup study of pregnant women (n = 17,000) at the Obstetrical and Gynecological Hospital to identify a risk score for bad outcomes. Several papers have been written, and others are in preparation. During 1988, a randomized controlled clinical trial of social support during pregnancy will be started.

India: Collaboration on reproductive and contraceptive research between NICHD and the Indian Council for Medical Research (ICMR) has continued under the auspices of the Indo-U.S. Subcommission on Science and Technology, mandated by the Indo-U.S. Bilateral Agreement, and under the Indo-U.S. Science and Technology Initiative. NICHD and ICMR jointly sponsored the Indo-U.S. Workshop on Pharmaceutical Technology and Bioavailability Present and Future, which was held in New Delhi November 10–14, 1986. This workshop was attended by scientists from the public and private sectors who have an interest in, and are responsible for, contraceptive drug development. On February 9–11, 1987, the Fifth Indo-U.S. Workshop on Reproduction and Contraception Research was held in New Delhi. During this workshop, the participants developed an agenda that will guide collaborative research during the next 18 months. In addition to the two workshops, ICMR has initiated studies with the biodegradable implant contraceptive drug delivery system called Capronor TM. NICHD has assisted ICMR in providing background information on contraceptive monitoring and surveillance, which the Ministry of Health plans to implement in India. NICHD continues to fund the U.S. component of the Indo-U.S. Science and Technology Initiative, which deals primarily with the development of antifertility vaccines.

Israel: In collaboration with the Ben Gurion University in Berr Sheva, Israel, NICHD has engaged in a study of infant feeding practices among Bedouin women to determine the relationship of changes in infant feeding practices during the first year of life

to physical growth and development and respiratory and gastrointestinal diseases of infancy. The data collection for this study is completed, and its analysis is in progress in collaboration with investigators from the Ben Gurion University.

Another study is examining, among a population of North African Jewish women who live in Israel, maternal nutritional status in relation to choices of infant feeding practices at birth and changes during the first year of life. Infants from this study are followed until 30 months of age to obtain information on physical growth and development. Data collection for this project is almost complete.

Japan: NICHD has participated in the Malnutrition Panel of the U.S.-Japan Program since 1966. The Malnutrition Panel's research objectives have shifted since then from the broad goal of reducing the prevalence of malnutrition, especially in Asia, to more specific goals, such as ascertaining the effects of changing food patterns on disease and determining the effects of malnutrition during pregnancy, infancy, and childhood on lactation, reproduction, work performance, and social competence. Although Asia remains the primary area of interest, research in other developing countries of the Pacific Basin is funded under the auspices of the U.S.-Japan Malnutrition Panel. In FY 1987, one NICHD-supported research project was designated a U.S.-Japan project. This grant, to an investigator at Case Western Reserve University, involves nutrition studies performed in groups of infants and children living in Costa Rica.

Pakistan: NICHD has developed a study of pregnancy outcome in four different areas of Pakistan with the Aga Kahn University in Karachi. The project will involve the collection of information about risk factors associated with preterm delivery and intrauterine growth retardation. The study population of pregnant women will be followed to delivery and children will be followed for 2 years to determine the contributions of preterm delivery and intrauterine growth retardation to morbidity and mortality during the first 2 years of life.

Spain: NICHD began working with the School of Public Health in Granada in the summer of 1987 on a program project for health services research in maternal and child health. The first step is the organization of a population base summary data collection form for all deliveries in the region (about 100,000 per year). A group of specific research projects will be initiated during 1988, including a teaching component. The Institute will work collaboratively with Spanish counterparts on the collection and analysis of data of mutual interest.

Activities With International and Multinational Organizations

European Medical Research Council: Interest in the activities of the European Medical Research Council (EMRC) Advisory Subgroup on Human Reproduction and attendance at its meetings have continued. This EMRC Advisory Subgroup identifies areas for cooperation within Europe and between Europe and the United States on research in reproduction. It also interacts with the pharmaceutical companies in order to obtain information about any of their research projects that might have a bearing on human reproduction. NICHD staff attended the meeting of the Advisory Subgroup on Human Reproduction, which was held December 5, 1986, in Geneva, Switzerland, to discuss future research needs in the field of reproductive biology for the European countries. The areas concentrated on were sexually transmitted diseases and their impact on reproduction, DNA technology in reproductive research, and human *in vitro* fertilization research needs.

International Collaborative Effort on Perinatal and Infant Mortality: NICHD staff participated in meetings of the planning group for the International Collaborative Effort on Perinatal and Infant Mortality (ICE). The planning group is coordinated through the Office of International Statistics, National Center for Health Statistics. In addition, ICE consists of two representatives from each of the following member countries: Denmark, England and Wales, Federal Republic of Germany, Israel, Japan, Norway, Scotland, and Sweden. Representatives from the following countries have also attended planning group meetings: Australia, China, Finland, and Holland. The European Office of the World Health Organization has also participated in ICE meetings.

World Health Organization: NICHD continues to have extensive interactions with the World Health Organization (WHO) special Program of Research, Development, and Research Training in Human Reproduction (HRP). Collaborative research on the development of new contraceptive modalities has made good progress. HRP has begun Phase II clinical studies with a long-acting drug and an implant for female fertility regulation. NICHD has provided support for the development of both of these entities. Additionally, the two organizations have collaborated on the development of a long-acting injectable androgen that holds promise for male fertility regulation. The staff

of NICHD continue to serve as Collaborating Program Scientists on the various steering committees of HRP, including:

- Task Force on Male Methods of Fertility Regulation;
- Task Force on Post-Ovulatory Drugs;
- Task Force on Safety and Efficacy of Fertility Regulating Methods; and
- Task Force on Behavioral and Social Determinants of Fertility Regulation.

Extramural Programs

Canada: Sudden infant death syndrome (SIDS) is a leading cause of death under 1 year of age. The etiology and pathogenesis of the syndrome are unknown, but the leading hypothesis considers the existence of a defect in respiratory control mechanism. A team of investigators in Toronto is attempting to link and relate morphologic and histochemical information obtained from all components (central and peripheral) of the respiratory control mechanism in the same victim.

Costa Rica: Iron deficiency is the most common single-nutrient deficiency, estimated to affect up to 25 percent of infants worldwide. In collaboration with investigators in Costa Rica, an investigator at Case Western Reserve University has been studying whether iron therapy corrects the developmental deficits and behavioral abnormalities associated with iron deficiency anemia in infancy.

Finland: An American investigator, in collaboration with a Finnish colleague, is carrying out a study in high-risk pregnant diabetic patients to define hyperinsulinemia and its possible role in macrosomia (large size infants). For this purpose, they are determining the concentrations of glucose, insulin, and C-peptide in amniotic fluid and umbilical venous plasma. In preliminary results, no abnormal values were found for insulin antibodies in amniotic fluids of the chemical diabetic group. For the Type 1 diabetic group, insulin antibody levels in both umbilical venous plasma and amniotic fluid were significantly greater than in the nondiabetic controls.

Guatemala: From 1969 to 1977, the Institute of Nutrition Central America and Panama (INCAP) carried out a longitudinal nutritional intervention program in four rural communities in Panama. The results indicated that a carefully controlled nutrition supplementation program could reverse, to a significant degree, the effects of malnutrition on physical growth and mental development in preschool children. Whether or not the immediate benefits of this program persist into later life is unknown.

A multidisciplinary research team from Stanford and Cornell Universities is now collaborating with INCAP on a cross-sectional study of adolescents in these four communities and in two others that did not participate in the study. Body size, work capacity, maturation, intellectual function, and school performance will be assessed. If the data indicate that an investment in nutrition in early life leads to young people with a greater potential for healthy, productive lives, the results will have important implications for program planning in public health.

Mexico: A research program project at the University of Texas Health Science Center in Houston is investigating the interactions of specific components of human milk in the lumens of the gastrointestinal and respiratory tracts that result in protection of the infant from bacterial or viral disease. Samples of milk, stool, and blood are being collected from lactating women and their infants in Houston and Mexico City and correlated for mechanistic and epidemiologic studies.

New Zealand: An investigator in New Zealand is working to elucidate the three-dimensional structure of human lactoferrin, the major iron-binding protein in milk, many other body secretions, and leukocytes. The broad aim of this project is to gain a better understanding of the antibacterial properties of lactoferrin and the mechanisms by which it takes up and releases metal ions. This should have important implications for understanding body defense mechanisms, the biology of human milk, and the bioavailability of trace elements.

Norway: A study of successive small-for-gestational-age births is being supported in Norway. A companion project has also been funded with the University of Alabama in Birmingham in the United States. This research project is a prospective study to determine risk factors that will distinguish mothers who have repeated SGA births from those mothers who have a single, unexpected SGA birth.

Philippines: This project focuses on the epidemiology of infant feeding practices and the consequences of changes in infant feeding behavior in low-income countries. The study involves an analysis of a sample of approximately 3,100 mother-infant pairs, using data gathered from a survey of Filipino fami-

lies. The survey has followed these families, gathering information on a bimonthly basis from the last trimester of the mothers' pregnancy through the second year of the infants' lives.

United Kingdom: An American team, in cooperation with British investigators, is examining the development of sleep-state organization in normal infants and infants at risk for the SIDS. The English team has obtained 17,000 24-hour recordings from infants who were born in a single year in London; of these, 22 subsequently died of SIDS.

International Conferences, Seminars, and Meetings

The Ninth International Workshop on Human Gene Mapping was held in Paris, France, September 6–11, 1987. NICHD, together with seven other institutes, helped support the participation of several American investigators. Among the important functions of the gene mapping meetings have been continued standardization of mapping criteria, the expert and critical evaluation and compilation of the voluminous mapping data, the maintenance of a standard system of nomenclature for human genes, and the assignment of gene symbols. The meetings also foster rapid exchange of information and ideas among workers from all parts of the world.

NICHD staff presented data at the International Conference on Cardiovascular Disease Risk in Women, which was held in London in July. Their presentations included analyses of data from "The Walnut Creek Contraceptive Drug Study," which was funded by NICHD. This was a large, observational cohort study concerned with the medical effects of contraceptive steroids and other methods of fertility control. Medical histories and physical examinations were administered through 1977, but a followup mortality search was conducted through the mid-1980s. A great many of the women included in this study had gone through the menopause by this time. Analyses of the Walnut Creek Study data in 1987 showed that women who have used a steroid hormone in the past have no better or poorer cardiovascular risk profile, compared to nonusers, as defined by the NIH Consensus Development Conference on Lowering Blood Cholesterol in Women.

Intramural Programs and Activities

Scientists in the NICHD intramural research program engage in extensive international collaboration on research projects relevant to their own research interest at the NIH. Often these collaborations endure for many years. The major emphasis of the NICHD intramural research program is on basic and clinically applied research in the broad area of developmental biology. Areas presently being examined include:

- Developmental endocrinology;
- Reproductive biology;
- Cellular differentiation;
- Human genetics and inborn metabolic errors;
- Molecular endocrinology;
- Developmental and molecular immunity;
- Developmental neurobiology;
- Molecular genetics;
- Pharmacogenetics;
- Growth factors;
- Neurochemistry and neuroimmunology;
- Theoretical and physical biology;
- Cell biology and metabolism; and
- Comparative ethology.

In all of these areas, NICHD intramural scientists have spent considerable time in foreign laboratories, and scientists from many other countries have used NIH resources while making significant contributions to the Institute's research.

Laboratory of Molecular Genetics: The Laboratory of Molecular Genetics has numerous scientists from foreign countries among its researchers at the postdoctoral and senior levels. This includes workers from Austria, Belgium, China, France, Federal Republic of Germany (FRG), Hungary, India, Israel, Italy, Japan, Switzerland, and United Kingdom. Several groups in the Laboratory have ongoing collaborations with scientists abroad.

Members of the Laboratory participated in international conferences and visited institutes in various countries including Austria, China, France, FRG, Greece, Israel, Italy, Japan, Netherlands, Spain, and United Kingdom. In 1988 the Laboratory will host a major international conference at the Lister Hill Center on the "Molecular Genetics of Development."

Laboratory of Developmental Neurobiology: Scientists from several nations—including Australia, China, Czechoslovakia, FRG, Israel, Japan, Spain, and United Kingdom—either are currently in the Laboratory of Developmental Neurobiology or have made arrangements to work there. Members of the Laboratory have participated in international meetings in

France, Hungary, Mexico, Spain, United Kingdom, and U.S.S.R. The Laboratory has collaborative interactions involving contract or other mechanisms with FRG and U.K. scientists. These interactions with the international scientific community play a vital role in the program of the Laboratory.

Laboratory of Neurochemistry and Neuroimmunology: Scientists in the Laboratory of Neurochemistry and Neuroimmunology are involved in collaborations with several laboratories abroad, largely in the area of immunocytochemistry. The Laboratory has produced a number of monoclonal and specific polyclonal antibodies, which are particularly useful in tracing peptidergic neuronal pathways in the central nervous system. These antibodies are being used in experiments in:

- Canada (University of Ottawa);
- Denmark (University of Copenhagen);
- England (Oxford University, University of London);
- Israel (Hebrew University of Jerusalem);
- Netherlands (Netherlands Brain Research Institute, University of Utrecht); and
- Wales (University of Wales).

The Laboratory has several Visiting Fellows and senior scientists from Argentina, China, New Zealand, and Turkey. It also has ongoing collaborative research on a project concerning neuropeptides and stress with a scientist at Lund University, Sweden, and on prohormone converting enzymes with an investigator in France. Polyclonal antibodies to neuropeptides and their precursors produced by the Laboratory have been supplied to scientists in Israel and England for immunochemical studies.

Members of the Laboratory have participated in international meetings and visited institutes in Denmark, France, FRG, Hong Kong, Netherlands, Singapore and Switzerland.

Laboratory of Developmental Pharmacology: The Laboratory of Developmental Pharmacology studies the biological mechanisms by which genes affect the metabolism of drugs and environmental chemicals. Knowledge of these genes, and the enzymes that they encode, may be important in predicting which individuals are at risk for chemically induced tumors, drug toxicity, and birth defects. The Laboratory is currently cooperating with many foreign laboratories such as:

- Tumor Research Laboratory, Fujian Medical College, China;
- Department of Genetics, Institute for Cancer Research, Norwegian Radium Hospital, Oslo, Norway;
- Fibiger Institute, Copenhagen, Denmark;
- Institut Pasteur, Paris, France;
- Department of Clinical Pharmacology, Flinders Medical Centre, Adelaide, Australia;
- Centre National de la Recherche Scientifique, Gif-Sur-Yvette, France; and
- Department of Genetics, University of Alberta, Edmonton, Canada.

Developmental Endocrinology Branch: The Developmental Endocrinology Branch conducts clinical and basic laboratory studies of endocrine disorders involving the adrenal, ovary, pituitary, and testicle. Visiting Fellows and Scientists from many countries participate several times each week in clinical conferences, medical rounds, and outpatient clinics under the supervision of senior staff physicians. Foreign physicians participate in basic laboratory or clinical research under the supervision of at least one senior staff member. During the past year, the Branch has had 23 such visitors from abroad. The countries of origin include: Argentina, Australia, Brazil, Canada, Chile, China, France, FRG, Greece, India, Ireland, Italy, Japan, Sudan, and United Kingdom. The projects in which they have played major roles include:

- Stress-induced steroid biosynthesis;
- Cloning of the gene for an abnormal glucocorticoid receptor;
- Role of progesterone in implantation;
- Treatment of precocious puberty;
- Molecular heterogeneity of human chorionic gonadotropin (hCG);
- Development of radioimmunoassay (RIA) and new bioassays for circulating growth factors;
- Neonatal pituitary-gonadal function;
- Mechanism of long bone growth;
- Studies of sperm function and biology in infertile men;
- Cushing's syndrome;
- Study of secretory endometrial peptides;
- Physiologic study of choriogonadotropin-related molecules as markers of disease; and

- Study of heterogeneous forms of choriogonadotropin produced by testicular neoplasms.

Ongoing collaborative efforts have been established with:

- Children's Hospital in Buenos Aires, Argentina, to study the etiology of ambiguous genitalia in children;
- Institute of Nutrition and Food Technology at the University of Chile, to investigate hypothalamic releasing factors in infant malnutrition;
- Beijing Medical College Hospital, to investigate gonadotroph morphology;
- University of Catania, Italy, to describe ectopic pro-opiomelanocortin (POMC) secretion;
- University of Santiago, Chile, to study the hypothalamic-pituitary-adrenal axis in malnutrition; and
- Institute of Child Health in Athens, Greece, to explore the effects of prenatal phenobarbital exposure on puberty and adolescence.

Branch senior staff organized two international meetings in 1987: the International Conference on Recent Advances in Adrenal Regulation and Function (Madrid) and the International Conference on the Mechanisms of Physical and Emotional Stress (Bethesda, Maryland).

Laboratory of Theoretical and Physical Biology: The Laboratory of Theoretical and Physical Biology is engaged in collaborative research with several laboratories throughout the world. A scientist of the Unit of Endocrinology, University of Florence, Italy, is continuing and expanding studies he began in the Laboratory regarding the characterization of receptors for oxytocin and vasopressin in the male and female genital tract. An investigator at the Institute for Pharmacological Research Mario Negri, Milan, Italy, is continuing and extending studies that he also began in the Laboratory regarding mathematical methods for objective evaluation of frequency of hormonal pulses, with special reference to luteinizing hormone (LH) and reproductive physiology. A Laboratory scientist is collaborating with groups in Belgium, France, and Israel regarding the use of thermal ionization mass spectrometry for study of calcium metabolism in man and thermospray liquid chromatography-mass spectrometry of steroids. During the past year, the Laboratory has hosted Visiting Scientists from Argentina, Austria, China, FRG, Hungary, Italy, Mexico, United Kingdom, Yugoslavia and Taiwan. The Laboratory has distributed a series of computer programs to hundreds of scientists in dozens of countries, and several scientists from countries throughout the world have come to the Laboratory, for a short stay, to become familiar with the principles of operation of these computer programs and interpretation of results.

A Laboratory scientist has been active on the Council of the International Electrophoresis Society and has attended its meetings in London. He also has been attending the German Electrophoresis Society meetings on an annual basis. Other Laboratory scientists have been active in international gatherings, including meetings in FRG, Japan, Switzerland, and United Kingdom.

Laboratory of Comparative Ethology: Scientists in the Laboratory of Comparative Ethology have been carrying out a number of long-term collaborative studies with research teams from 11 countries in Europe, Asia, and Central America. These studies include longitudinal, cross-cultural investigations of linguistic, cognitive, and social-emotional development in human infants and both laboratory and field studies of biobehavioral development in several nonhuman primate species.

One major collaborative study has been examining the relationship between patterns of mother-infant interaction and the emergence of language at the end of the first year of life among infants studied in India (at the Center for Advanced Study in Psychology, Orissa Province), France (at the Centre National de la Recherche Scientifique in Paris), FRG (at the Max Planck Institute for Psychiatry in Munich), Japan (at Shurya University in Tokyo), and in the United States. A second collaborative study between researchers at the Max-Planck Institute for Psychiatry and the Laboratory is investigating vocal production and perception in preverbal human infants from different cultures, using sound spectrographic analytic techniques derived from parallel studies of nonhuman primate infants in the Laboratory. A third series of collaborative studies focuses on the effects of various day-care arrangements on the social, emotional, and cognitive development of infants and toddlers in Sweden (University of Goteborg), Israel (University of Haifa), Japan (Hokkaido University), and Singapore (Research Department, Ministry of Community Development). The Laboratory also has continued a longstanding project in which psychological aspects of human childbirth are compared among primiparous parents in Denmark and the United States. Finally, this past year a study of reunion behavior between toddlers and their parents at a day-care center in Wuhan, Hubei, China was completed in collaboration with researchers at the Ton Ji Medical University. Collaborative studies with foreign investigators on various aspects of biobehavioral

development in nonhuman primate species have included:

- Field study of squirrel monkeys in Costa Rica (in collaboration with the Department of Zoology, University of Costa Rica);
- Investigation of the development of object manipulation and tool use in hand-reared capuchin monkeys (carried out at the Instituto di Psicologia, Consiglio Nazionale delle Ricerche, Rome, Italy); and
- Comparative studies of vocal ontogeny in New World monkeys using analytic techniques developed with colleagues at the Free University in Berlin. These collaborative projects will be continued in the coming year.

In FY 1987, Laboratory scientists also participated in international scientific workshops and meetings in China, Denmark, FRG, Italy, Japan, Sweden, and United Kingdom. Finally, the Laboratory continued its active support of the Fogarty international program, with Fellows from China, FRG, Jamaica, and Zaire carrying out research projects at the NIH.

Human Genetics Branch: The Human Genetics Branch has maintained close ties with the international scientific community in the training of foreign scientists and in extensive collaborative research efforts. A Visiting Scientist from Nigeria has discovered a new pathway of expression for the Alu gene family, the most ubiquitous gene present in vertebrates. Studies by a Visiting Fellow from Spain have led to the isolation and characterization of two newly described classes of RNA processing nuclease, efforts representing the first such discoveries in this field. A Visiting Fellow from the Netherlands has begun to study certain specific details relating to the structure and design of one of these enzymes, a complex, very large, subcellular particle. A Visiting Fellow from Spain has recently opened up a new area of research in the transport of mRNA from the nucleus of eukaryotic cells by developing methodology to study the process and by discovering how this process can be modulated.

In collaboration with scientists from Italy, laboratory staff successfully cloned and sequenced the cDNA encoding human glucose-6-phosphate dehydrogenase, the first isolation of this important gene product. Studies continue on the definition of the control regions of the gene itself. Other collaborative efforts have yielded the identification of complex splicing patterns involving genes that map to the G6PD locus, suggesting a dense packing of genetic information within this portion of the X chromosome. A Visiting Fellow from Italy is exploring the structure-function relationships of uteroglobin using recombinant DNA methodology. These efforts are being conducted to explain the potent anti phospholipase A2 activity of the protein, which can be found within the epithelial tissues of many vertebrates.

In collaboration with scientists from Finland, the mechanism of Salla disease was identified and found to be a disorder of sialic acid transport from lysosomes. Studies continue to elucidate further the nature of the transport defect and to determine how the human kidney treats free sialic acid. A Visiting Fellow from Australia has studied the nature of proteoglycans and the enzyme nucleotide pyrophosphatase in patients with Lowe syndrome, a disorder postulated to involve a biochemical defect in proteoglycan biosynthesis. A scientist from China has attempted to isolate the gene encoding the defective product in cystinosis, a rare disorder of cystine mobilization from lysosomes. A Visiting Scientist from Spain identified a lysosomal carrier system for the transport of tyrosine in rat thryoid cells. The mechanism may have a fundamental role in thryoxine biosynthesis. Members of the Branch have collaborated with colleagues in Canada on the first description of pancreatic involvement in cystinosis and with scientists in the Netherlands on the role that transamination plays in degrading methionine in a very rare methionine adenosyltransferase-deficient patient. Both these efforts resulted in publications. Members of the Branch also are working with Israeli scientists on the effects of lysosomal cystine loading on plasma membrane transport by renal tubular cells in culture.

Scientists from China have been engaged in the cloning of several of the alkaline phosphatase genes of man, the placental and the liver-bone-kidney forms. A Visiting Fellow from Japan has explored the controls over the expression of several proto-oncogenes in placental and liver cells. In addition, scientists from the Human Genetics Branch maintain active scientific collaborations with scientists from Australia, China, Finland, France, FRG, Israel, Italy, Japan, Netherlands, Spain, and United Kingdom, frequently exchanging reagents and unpublished data.

Laboratory of Developmental and Molecular Immunity: The Laboratory of Developmental and Molecular Immunity has hosted Visiting Scientists and Guest Researchers from China, Denmark, Egypt, Israel, Japan, Korea, New Zealand, and Sweden. These investigators have participated in ongoing research programs that include the characterization of bacterial pathogenesis and immunity, examination of the structural and functional role of the major histocompatibility antigens, and mechanisms regulat-

ing immune response at the cellular level. The activities of these research programs have led to presentation of data at international meetings held in Denmark, Japan, Spain, Sweden, and United Kingdom and have resulted in publication of several foreign-language manuscripts.

Active involvement of the Laboratory staff in vaccine development and field trials has led to several important international collaborative studies. In cooperation with investigators at the Bar-Ilan University in Israel, studies are in progress on the pathogenesis of *Staphylococcus aureus* infections. In collaboration with scientists at the South African Institute of Medical Research, the Public Health Authority of Nepal, the All-India Institute of Medical Sciences in New Delhi, the Shanghai Institute of Vaccines, and the National Institute for Vaccines and Sera in Beijing, the Laboratory has initiated a study aimed at developing the Vi capsule polysaccharide as a vaccine for prevention of typhoid fever.

The Section on Bacterial Disease Pathogenesis and Immunity has an especially extensive and active collaboration in Nepal to study both the pathogenesis of, and vaccine-induced immunity to, typhoid fever. Since this study established, for the first time, that vaccine-induced serum antibodies to the Vi capsular polysaccharide of *Salmonella typhi* can prevent invasive disease caused by this organism (typhoid fever), studies are being extended to *Salmonella paratyphi* A. In addition, these principles of inducing immunity with purified, standardized, surface antigens of Salmonella are being extended to other enteric bacterial pathogens that are invasive. The establishment of a comprehensive surveillance system, including laboratory facilities, in Nepal will facilitate this collaboration. Nepal has an unusually high incidence of enteric diseases and has provided a convenient site and reliable collaborators for studying both immunity and vaccine effects with reagents made in this Laboratory. The Laboratory also plans to study the age-related immunity and disease susceptibility of children to typhoid fever in India.

The Laboratory is expanding its studies for Phase II and Phase III (effectiveness) evaluation of the new acellular pertussis toxoid vaccine, composed solely of highly purified hydrogen peroxide-inactivated pertussis toxin, in Sweden. Sweden offers an unusual opportunity to study new pertussis vaccines because it has not immunized its population against pertussis since 1978, and it has an excellent, reliable surveillance program to monitor the unusually high incidence of this respiratory disease.

The Laboratory has a collaboration with the State Serum Institute of Copenhagen, Denmark, to study non-species-specific protective antigens in pneumococcus that could assist in inducing vaccine immunity to the acute respiratory diseases of infants and children, as well as immunocompromised adults, caused by this bacterial pathogen.

Finally, encapsulated bacterial diseases in infants and children (including *Haemophilus influenzae* type b and pneumococcus) are under study in collaboration with scientists at the University of Goteborg, Sweden. The immunogenicity and role of the capsular polysaccharide in prevention of these diseases are under investigation.

Endocrinology and Reproduction Research Branch: During 1987, investigators in the Endocrinology and Reproduction Research Branch have maintained collaborative research programs with scientists in Australia, FRG, Hungary, India, Italy, Japan, and New Zealand. Studies on localization and actions of angiotensin II and other neuropeptides in the kidney have been extended in joint studies with the Department of Medicine, Melbourne University. Also, a Guest Researcher from Wellington School of Medicine, New Zealand, has participated in studies on the expression of mRNA for angiotensin II receptors from the bovine adrenal gland, by *in situ* translation in Xenopus oocytes. The control of aldosterone secretion by angiotensin II, and the pathways of inositol polyphosphate production and metabolism in adrenal glomerulosa cells, are being studied by a Visiting Fellow from the Department of Physiology at Semmelweis University Medical School, Budapest, Hungary, with whom a joint program on the receptors and actions of inositol triphosphate (IP_3) is maintained. This work is defining the relationship between IP_3 binding to specific microsomal receptors and the mobilization of calcium from intracellular stores during the steroidogenic action of angiotensin. The interactions between GnRH and gonadal steroids in the control of pituitary function have been studied in collaboration with the Department of Medicine at the University of Lubeck, to analyze the receptor-mediated inhibitory and stimulatory actions of estrogens and progestin upon gonadotropin secretion. The actions of gonadotropin-releasing hormone, arachidonic acid, and progesterone antagonists upon placental function have been studied in collaboration with the All-India Institute of Medical Sciences. This work, which was performed in cultured human placental cells by a Guest Researcher from the Institute, revealed new aspects of the roles of progesterone and arachidonate metabolites in the control of placental hormone secretion. Studies on the role of opiates in pituitary and testicular function have been continued in collaboration with members

of the Department of Medicine at the University of Rome. Clinical studies are performed in Rome for evaluation of bioactive LH levels by methods developed in the Branch, and an Italian scientist visits Bethesda to pursue basic studies on the production and actions of opiate peptides in the testis.

During FY 1987, a Visiting Fellow from Taiwan worked on the purification, characterization, and deglycosylation of pregnant mare serum gonadotropin. More than 100 mg of the pure hormone was obtained. The hormone is given to the National Pituitary Agency of Hormone Distribution Program, National Institute of Diabetes and Digestive and Kidney Diseases, for distribution to both domestic and foreign scientific communities for their research use. The Fellow has also developed a highly sensitive method for carbohydrate composition analysis of glycoproteins and is working on specific conditions to cleave certain carbohydrate moieties in an attempt to study the role of carbohydrate structures in gonadotropic action.

The role of protein kinase C in the regulation of cellular functions is being studied in collaboration with members of the Centre de Neurochimie, Centre National de la Recherche Scientifique, Strasbourg, France. In this study, the Laboratory has focused on the identification of nuclear protein kinase C in an effort to define the role of this enzyme in the regulation of gene expression. A nuclear protein kinase C has been isolated and the biochemical and immunologic properties characterized. This enzyme appears to be distinguishable from the cytosolic enzyme in its response to the various effectors. This study should shed light on the role of protein kinase C in the regulation of nuclear functions.

The Branch also has provided research training to Visiting Fellows and Scientists from Australia, China, Israel, Japan, New Zealand, Syria, and Yugoslavia.

Cell Biology and Metabolism Branch: The Cell Biology and Metabolism Branch continues to be active in the support and training of postdoctoral fellows, representing the following countries:

- Argentina—A Visiting Associate is studying the assembly and cell biology of multicomponent membrane complexes.
- FRG—One Visiting Associate is studying the molecular biology of iron metabolism and translational control of human gene expression; one Fellow is studying the assembly of multicomponent receptor complexes.
- Israel—One Fellow is studying the genetic regulation of the T-cell antigen receptor.
- Italy—One Visiting Fellow is studying the molecular regulation of the expression of the human interleukin-2 receptor gene.
- Japan—One Fellow is studying the biochemical basis of T-cell function.
- Spain—One Fellow is studying the molecular basis of human iron metabolism; another Fellow is studying signal transduction in human T-cells.

The Branch has recently completed a 3-year joint cooperative research program supported by a U.S.-Spain cooperative grant. The Branch also has been awarded a North Atlantic Treaty Organization grant for cooperative research on human iron metabolism and hereditary hemochromatosis, carried on in collaboration with researchers at the University of Amsterdam in the Netherlands.

Members of the Branch have been invited lecturers at numerous international conferences and congresses.

Office of the Scientific Director:

Section on Growth Factors: The Office of the Scientific Director includes two laboratory sections. The Section on Growth Factors currently hosts four Japanese scientists and one Italian scientist, all at the postdoctoral level, who are studying various aspects of the action of nerve growth factor on the model system PC12. One aspect of the work focuses on the kinases that appear to mediate the intracellular actions of the factor. Another focuses on the various phenotypic changes induced by the factor on its target cells. A postdoctoral Fellow from the Weizmann Institute in Rehovot, Israel, is interested in the development of the neural marker, tetanus toxin binding sites, and how nerve growth factor induces the expression of the glycolipid comprising these sites. This study involves an active collaboration with an investigator in the Department of Neurobiology of the Weizmann Institute. Another ongoing collaboration, with a scientist at Kyowa Hakko Kogyo Co., Ltd., of Tokyo, Japan, has been directed toward an understanding of the action of a kinase inhibitor, K-252a, developed in Japan and studied as a specific inhibitor of the actions of nerve growth factor on PC12 cells. The actions of this inhibitor give promise of providing a unique insight into the mechanisms by which nerve growth factor acts. The Section will shortly welcome an investigator, recently Dean of the Medical School in Skopje, Yugoslavia, for a sabbatical year, and is engaged in discussions with a Russian scientist of the Academy of Sciences (U.S.S.R.) who plans to spend a month with this Section. He would like to consider specific aspects of protein

synthesis in PC12 cells as affected by nerve growth factor and the consequent phosphorylation of the EF-2 and S6 proteins of the protein synthetic system.

Section on Viruses and Cellular Biology: In the Section on Viruses and Cellular Biology, a Visiting Fellow from Japan is studying the molecular mechanisms by which viral encoded gene products determine whether or not cells transformed by viruses *in vitro* will be tumorigenic *in vivo*. A Visiting Associate from India is working on another aspect of this same problem and has identified an "antigrowth" factor from SV40-transformed cells that inhibits the proliferation of lymphocytes, natural killer cells, and macrophages, possibly explaining why these cells are so highly oncogenic *in vivo*. Visiting Fellows from Greece and Ireland, as well as a Guest Researcher on sabbatical from the Marine Biology Institute in Yugoslavia, are exploring the molecular mechanisms of mammalian mutagenesis, as well as DNA replication and repair. These studies depend on the use of the small DNA virus SV40, or SV40-based shuttle vectors, as probes with which to illuminate complex macromolecular processes in mammalian cells.

The NICHD visiting and guest researcher programs provide opportunities for postdoctoral fellows and senior scientists from abroad to conduct collaborative research and to receive research training on the Bethesda campus. More than 125 scientists from 46 countries are currently active in the 12 basic science Laboratories and Clinical Research Branches of NICHD through the Institute's intramural research program.

Chapter X
National Institute of Dental Research

Introduction

In 1948, the National Institute of Dental Research (NIDR) was established to improve the dental health of the American people. By conducting and supporting research and research training in such diverse disciplines as microbiology, immunology, pain, genetics, behavioral sciences, oncology, and other basic and clinical sciences, NIDR not only has improved the oral health in this country and abroad but has also furthered understanding of, and treatments for, numerous and varied disorders including acquired immunodeficiency syndrome (AIDS), diabetes mellitus, arthritis, and osteoporosis.

International collaborations have been crucial to the advances NIDR has fostered. Foreign Visiting Scientists, Associates, and Fellows have shared their expertise and greatly quickened the pace of research conducted at NIDR while learning techniques and gaining insight useful to studies carried out in their own countries. Intramural and extramural NIDR investigators working abroad or in collaboration with foreign scientists have similarly benefited from the mutual exchange of data and skills.

FY 1987 saw numerous accomplishments of dental scientists active in the international collaborative arena. These research advances already have produced tangible benefits to people of the United States and other nations and hold promise of further improving oral health throughout the world.

Highlights of Recent Scientific Advances Resulting From International Activities

Work by Visiting Scientists, Associates, and Fellows in the Laboratory of Developmental Biology and Anomalies has led to a new understanding of the function of basement membranes, which surround all blood vessels, glands, nerves, and muscles and hold the cells of a tissue in place. Basement membranes are important in prevention of the spread of infection, metastasis, wound healing, scarring, and nerve regeneration.

For tumor cells to metastasize, they must invade basement membranes. NIDR researchers, in collaboration with visiting investigators, have pinpointed the structure and role of many of the proteins that constitute basement membranes. They discovered that a synthetic mimic of one of these proteins hampers the spread of tumors in mice lungs, apparently by inhibiting the binding of tumor cells to basement membranes. In related research, the research team has developed a laboratory test that measures the invasiveness of tumor cells and can be used to test the effectiveness of anticancer drugs. Of particular importance is the fact that this test significantly reduces the need for animal studies.

Another protein synthesized from basement membrane prevents scarring and fosters nerve regeneration after spinal cord injury in laboratory studies. Clinical implications suggest that this protein may eventually make it possible to prevent paralysis by interfering with the development of scar tissue that results from this type of injury.

Research by a Visiting Associate collaborating with investigators in the Laboratory of Oral Biology and Physiology may aid victims of accidents or bone cancer. This foreign investigator helped isolate and characterize a protein called osteogenin that can prompt bone growth. He is currently trying to clone the protein in large quantities so it can be used to replace large segments of bone damaged by accidents or surgically removed as part of cancer treatment.

Other studies by a Visiting Fellow in this Laboratory may lead to more effective cancer treatments. This researcher has been investigating blood clotting factors and has discovered that one factor, called fibrinogen, links melanoma cancer cells in a web-like fashion. This cocoon of fibrinogen may protect tu-

mor cells from destruction by the immune system and may explain the body's inability to counter the rapid spread of this disease.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

India: Negotiations were undertaken in New Delhi with the Indian Council for Medical Research with the hope of acquiring rupee funds to support participation by Indian scientists in the World Health Organization (WHO) International Collaborative Study of Oral Health Outcomes. It is anticipated that the study will begin in FY 1988 and extend through FY 1990.

Italy: Under the auspices of the U.S.-Italy Memorandum of Understanding, plans have begun for a cooperative venture to study osteonectin variations in a number of human bone diseases. Research indicates that levels of osteonectin, a key protein manufactured in bone, are affected by several skeletal disorders. An Italian research team, using U.S.-produced antisera, has developed techniques to pinpoint physiologic changes in the osteonectin molecule. Their work may facilitate the diagnosis and treatment of many bone disorders including bone cancers and osteoporosis.

In addition, Italian and American scientists are awaiting funds in order to collaborate on a project to study genes from white blood cells that produce autoantibodies. Some of these antibodies have been used to isolate and characterize the antigens with which they react. The methodology used in the production of human monoclonal autoantibodies was developed by the Italian scientists while they were at the NIH as Visiting Fellows.

Mexico: As part of a scientific exchange agreement between the NIH and the Center for Research and Advanced Studies in Mexico, an NIDR researcher from the Neurobiology and Anesthesiology Branch taught a course in neuroanatomical methodology to graduate students at the National Polytechnic Institute, Mexico City. This NIDR investigator also collaborated with a Mexican Fogarty Scholar on a project that explored the chemicals involved in nerve transmission in the spinal cord. In another aspect of this collaborative exchange, a Mexican graduate student is currently a Guest Researcher at NIDR, where he is studying the chemicals in the spinal cord involved in processing pain signals.

Activities With International and Multinational Organizations

American Dental Association: The Assistant Director for International Health aided the new American Dental Association (ADA) Council on Scientific Programs and International Relations in drafting proposed ADA initiatives, and in facilitating dental participation in meetings of the National Council on International Health. She also provided reports on NIDR activities that especially highlighted NIDR's interactions with China (ADA maintains a special initiative with that country).

Committee on Data for Science and Technology: NIDR's Microbial Systematics Section is heavily involved in two computerized data banks of the Committee on Data for Science and Technology (CODATA): the CODATA/UISI Hybridoma Data bank, which provides information on monoclonal antibodies that are available, and the CODATA/WFCC/IUMS Microbial Strain Data Network, which locates organizations, companies, or researchers who have data on specific microbes. NIDR investigators organized a workshop on the Microbial Strain Data Network for the United Nations Environment Program and designed two training courses on computers and culture collections that were presented as a series in Brazil and Czechoslovakia. An NIDR researcher also consulted on international communication of strain data by the European Culture Collection Organization in Budapest and is the chairman of the CODATA/WFCC Task Group on Coordination of Macromolecular Sequence Banks. NIDR also was involved in the training of the Microbial Strain Data Network's Information Officer.

European Organization for Caries Research: During FY 1987, an NIDR scientist was awarded the European Organization for Caries Research (ORCA) Prize for his outstanding achievements in developing tooth decay prevention programs. The award was given at the 34th Congress of ORCA held in Budapest, Hungary. The Chief of the Epidemiology Branch in NIDR's Epidemiology and Oral Diseases Prevention Program also organized and directed a course entitled "Epidemiology: Methods and Applications" that was given at the ORCA Summer School of Cariology in Bergen, Norway.

Fédération Dentaire Internationale: The NIDR Director serves as a member of the Fédération Dentaire Internationale (FDI) Commission on Oral Health,

Research and Epidemiology. During this fiscal year, the Assistant Director for International Health served as consultant to the Scientific Program Committee, Chairman of the Working Group on Oral Health Promotion, and representative of Behavioral Scientists in Dental Research to the General Assembly of FDI. She also negotiated with FDI for space and time on the 1988 meeting agenda for NIDR's 40th anniversary activities.

An NIDR investigator was responsible for research aiding evaluation of FDI's scientific programs and membership services and also served on several FDI committees including the Oral Health Promotion Working Group, the Marketing Working Group, and the Scientific Program Committee. In addition, the extramural administrator responsible for Restorative Materials research served as vice-chairman of the Commission on Dental Products.

World Health Organization: NIDR continues to be highly involved in WHO's International Collaborative Study of Oral Health Outcomes (ICS-II). This multinational research protocol examines the relative impact of lifestyle, environment, and delivery of health services in determining the oral health of a population. WHO coordinates the study design, conduct, and analysis of the data collected from a variety of industrialized and middle-income developing countries that wish to collaborate on this oral health study.

During FY 1987, NIDR initiated or aided the development of ICS-II contract solicitations or grant submissions, working with the National Center for Health Services Research, the Indian Health Service, and the Centers for Disease Control. NIDR awarded a contract to WHO to help prepare a U.S. replication of the Baltimore area study in the ICS-II. Negotiations were held in New Delhi with WHO and the Indian Council for Medical Research, the Ministry of Health, and the principal investigator located in Chandegargh's Postgraduate Institute of Medical Research and Education. Plans are under way to initiate this project during FY 1988–90.

Israeli co-investigators also were provided technical assistance with their proposal for potential funding from the National Institute on Aging. The Assistant Director for International Health continued ICS-II negotiations in Cairo with the principal investigator and began negotiations with the U.S.S.R. WHO representative on potential U.S.-U.S.S.R. bilateral cooperation for ICS-II.

The Assistant Director also attended the Oral Health Research Review and Advisory Group meeting of WHO held in Manila, Philippines, and maintained coordination of NIDR as a WHO Collaborating Center. In addition, NIDR facilitated planning for WHO and Pan American Health Organization (PAHO) activities related to AIDS.

A member of the NIDR Science Transfer and Analysis Branch, Epidemiology and Oral Disease Prevention Program, was one of two lecturers who traveled to Chiang Mai, Thailand, to conduct a 2-week course on preventive dentistry at the Intercountry Centre for Oral Health in collaboration with WHO.

Extramural Programs

In FY 1987, NIDR funded four foreign grants and seven domestic grants with foreign components whose studies have contributed substantially to the progress of dental research, covering such diverse areas as tooth decay and gum disease, cleft lip and palate disorders, and the oral side effects of drugs. Researchers at the University of Alabama in Birmingham collaborating with investigators at the Universidad Peruana, Cayetario Herdia in Lima, Peru, discovered that chronic malnutrition can heighten children's susceptibility to decay and delay the eruption of baby teeth. Such a delay in appearance of baby teeth can make it difficult for children to eat properly and thereby intensify their malnutrition. These findings may influence the development of public health policies of numerous countries and will foster the design of optimum strategies to prevent oral diseases in children.

Investigators at the University of Oklahoma Health Sciences Center, in collaboration with researchers at the Dental Research Unit of the Royal College of Surgeons of England in London, are studying the various virulence components of the cavity-promoting microbe *Streptococcus mutans*. Their research, which should provide important information about the genetic regulation of these virulence factors, is aimed at designing proteins that may be good candidates for a caries vaccine.

An NIDR-supported scientist at the University of California in Los Angeles conducted a study in Shanghai, China, that has furthered understanding of cleft lip and palate disorders and will provide a basis for the effective genetic counseling of oriental families at risk of having a clefted infant. Preliminary findings from this study indicate that cleft lip with or without cleft palate is caused by a single gene in this population. This gene seems to put a fetus at risk of developing the disorder if it is exposed to specific environmental factors.

Another investigator at Indiana University is using dental records and casts obtained by a dentist at the

Beijing Medical College in China to distinguish between the influence of genetics and environmental factors on dental traits such as tooth size and bite. These dental records offer a valuable opportunity to study a complex problem because nutrition—a major environmental factor—is highly dependent on family income among the individuals being studied.

Researchers at McGill University in Montreal, Canada, are exploring the natural course of gum disease by conducting an investigation of the periodontal status of Tecumseh, Michigan, residents who were enrolled in an epidemiologic study carried out by dental scientists in 1959–60. The findings from this research will broaden understanding of the natural history of gum disease and may identify opportunities for prevention.

Researchers at the University of Maryland in Baltimore are collaborating with investigators at West Falische-Wilhelms Universitat in Munster, Federal Republic of Germany (FRG), and the University of Basel in Switzerland on a clinical study of the effects on gums of cyclosporin A, an immune system suppressant. This drug is used extensively in Europe and Japan to treat patients with autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, and lupus erythematosus, but in the United States cyclosporin A is approved for use only in preventing rejection of organ transplants. Because large doses of cyclosporin A are linked to significant side effects including excessive gum growth, studies are needed to assess the highest dosage of cyclosporin A permissible without serious side effects. The findings of this study may expand the use of cyclosporin A in the United States.

Investigators at the University of California are using old filling materials removed from extracted teeth in a Dutch clinical study to assess what forces of the mouth and teeth affect the structure of the materials used in the fillings. This research will ultimately lead to the development of biomaterials with better wear resistance.

International Conferences, Seminars, and Meetings

In FY 1987, 111 NIDR scientists participated in 75 conferences, symposia, collaborative research meetings, and seminars in 19 countries throughout the world.

In an effort to foster Egypt-Israel cooperative research projects, the Assistant Director for International Health took part in a special meeting on Egyptian-Israeli participation in the Agency for International Development Regional Cooperation Program. At the meeting, held at the National Academy of Sciences in Washington, D.C., the Assistant Director expanded on WHO's ICS-II program as a potential avenue for Egypt-Israel joint research ventures.

During this fiscal year, the Assistant Director participated in the Oral Health Research Review and Advisory Group meeting of WHO held in Manila. At the World Dental Congress, also held in Manila, the Assistant Director organized a special session on lowering barriers to dental care, chaired the Working Group on Oral Health Promotion, produced draft guidelines for national dental associations, served on the Scientific Program Committee, consulted with the Commission on Oral Research and Epidemiology, and represented the Behavioral Scientists in Dental Research at the General Assembly. The Assistant Director also presented a paper on converting unmet need for dental care to effective demand.

At the International Sociological Association meeting in New Delhi, India, the Assistant Director for International Health presented a paper on the International Collaborative Study of Oral Health Outcomes. The Assistant Director also attended a National Council on International Health seminar on health needs as perceived by less developed countries.

NIDR is a leading world center for pain research, and several NIDR researchers presented papers at the annual meeting of the International Association for the Study of Pain held in Hamburg, FRG. NIDR investigators also participated in a workshop on extracellular matrix and cell differentiation in Genoa, Italy, and attended the International Conference on Calcium Regulation, Hormones, and Bone Metabolism held in Nice, France.

Other major meetings in which NIDR scientists participated include:

- Pan-American Congress on Rheumatism in Buenos Aires, Argentina;
- Nobel Conference on Diabetes in Stockholm, Sweden;
- Symposium on Proteoglycans, held in locations in the Federal Republic of Germany, Czechoslovakia, Hungary, and France;
- Fourth Symposium on Inflammation Markers in Lyons, France;
- Symposium on Autoimmune Disorders in Zagreb, Yugoslavia;
- Conference on Tumor Necrosis in Heidelberg, FRG, and London, England; and

- Royal Microbiology Society meeting in York, England.

In addition, NIDR was represented at the Third International Conference on AIDS in Washington, D.C., the 34th Congress of the European Organization for Caries Research in Budapest, and the Symposium on Neurogenic Trigeminal Pain in Goteborg, Sweden.

The Director of NIDR visited China, where he discussed collaborative studies in oral disease prevention in various Chinese communities. He also lectured in Beijing and Xian on clinical trials and population studies, including longitudinal research methodology regarding preventive dentistry technologies.

Of special concern and interest to the Chinese were potential collaborative trials regarding the prevention of tooth decay at the root surface and anticalculus agents that act against the buildup of hard mineral deposits on teeth. The Director was awarded an Honorary Professorship at the Medical Sciences University of Beijing. This is only the second time in history that this honor has been conferred on a foreigner.

In Stockholm, Sweden, the Director presented a paper on future research on oral diseases at a symposium entitled "Oral Health During the Nineties." He also presented a paper on the epidemiology of periodontal disease in adults at the 1987 joint meeting of the Swiss Society of Periodontology and the Dutch Society of Periodontology in Montreux, Switzerland. In addition, the Director lectured at the University of Bergen, Norway, and was one of a prominent panel of international scientists who evaluated the future direction of dental research in Norway, supported by the Norwegian Research Council for Science and the Humanities.

An NIDR epidemiology specialist served as a Visiting Professor at the University of Umea, Sweden, where he gave seminars on tooth decay prediction models and consulted with faculty on specific research projects with an emphasis on predicting tooth decay in large populations. These predictions enable public health services to target their tooth decay prevention tactics more effectively.

A member of the Science Transfer and Research Analysis Branch serves as a consultant to the Canadian Government regarding its oral health promotion agenda. In that capacity, she participated in a 2-day planning meeting in Ottawa.

In FY 1987, 31 scientists from NIDR presented papers and participated in poster sessions at the annual meeting of the International Association for Dental Research in Chicago.

Intramural Programs and Activities

Intramural Program: In FY 1987, the Institute's intramural research program hosted 58 scientists from 21 countries: Australia, Belgium, Canada, China, Denmark, Finland, France, FRG, India, Israel, Italy, Japan, Korea, Luxembourg, New Zealand, Norway, Spain, Switzerland, United Kingdom, U.S.S.R., and Taiwan.

In the Laboratory of Oral Biology and Physiology, a French Guest Researcher and Italian Visiting Associate discovered differences between the cross-linking occurring in the skin surface cells of normal individuals and psoriasis patients. These findings may lead to more effective treatments for psoriasis, a common skin disease.

A Belgian NIH Visiting Fellow working in this Laboratory is studying growth factors generated by cartilage that may prove useful in the treatment of arthritis and other bone disorders. Other studies in this Laboratory by an Italian Visiting Fellow indicate that the improper degradation of blood clots may contribute to the joint inflammation that arthritis patients experience.

During FY 1987, the Neurobiology and Anesthesiology Branch hosted five Visiting Scientists from Belgium, China, Israel, and Japan. Research by a Belgian Visiting Fellow done in collaboration with an intramural investigator reveals that opiates have peripheral nervous system actions in inflamed tissues in addition to their known central nervous system effects. These findings offer the exciting possibility of developing opiates that act exclusively on the peripheral nervous system, thus bypassing some of the serious side effects of opiate drugs.

Chinese and Japanese scientists collaborating with an intramural investigator have developed a rat model of a human nerve disorder whose hallmark is chronic burning pain. Studies are under way to pinpoint the role of various nerves in this condition with the hope of amassing findings that will lead to a treatment for this disorder. In other research, an Israeli Visiting Associate is using a computerized statistical analysis to discern the symptoms that typify various craniofacial and jaw pain disorders.

In FY 1987, the Bone Research Branch hosted Visiting Scientists, Fellows, and Associates from Australia, FRG, Japan, Spain, and United Kingdom. Most of these investigators are studying proteoglycans, bottle-brush-shaped molecules prevalent in connective tissues that are thought to play a major role in cell surface and intracellular membrane transport processes. Two Visiting Fellows also are exploring

the biochemistry of bone formation. Their findings should broaden understanding of bone growth and development in both health and disease.

An applied mathematician from the University of Beijing in China, working in collaboration with a researcher in the Diagnostics Systems Branch, has substantially improved the computerized reconstructions of radiographs of clinical diagnostic interest. Her work has made it possible to create dental tissue reconstructions that are relatively devoid of artifact contours common to the control reconstructions that were not corrected. The Diagnostics Systems Branch had two other Visiting Scientists. A dentist and accomplished computer programmer from Amsterdam in the Netherlands is trying to eliminate soft-tissue artifacts from images of bone and teeth, and an associate professor of oral and maxillofacial surgery from the Nippon Dental University in Japan is planning to extend his research in the use of nuclear medicine to characterize observed dynamics of bone loss caused by a variety of common diseases.

The Clinical Investigations and Patient Care Branch had five Visiting Scientists, Associates, or Fellows from Canada, China, India, Israel, Switzerland, and Taiwan. Studies by a Canadian Visiting Scientist have greatly contributed to the understanding of the ion transport events that foster the secretion of salivary fluid. This research has implications for the development of treatments for cystic fibrosis and salivary gland disorders. A Visiting Fellow from Israel is exploring the antimicrobial activity of the mucous membrane in the mouth, and a Visiting Associate from Taiwan is studying oral transmission of AIDS, as well as oral disorders associated with AIDS.

The Laboratory of Microbiology and Immunology had several Visiting Fellows, Associates, and Scientists from Australia, FRG, Israel, Japan, New Zealand, and Switzerland. An Israeli Visiting Scientist is studying growth factors that foster the production of mature white blood cells—research that may lead to drugs that boost a person's immune system. Another Israeli Visiting Fellow is studying the role that multispecies bacterial colonies play in the formation of dental plaque, and Australian and Japanese Fellows are examining the structure and function of secretory cells. In other research, a Japanese Visiting Scientist is producing monoclonal antibodies to a cell receptor that plays a key role in allergies. This work might lead to better treatments for allergic conditions.

A New Zealand Visiting Scientist and a German Visiting Associate are studying the regulation of sugar transport and metabolism in bacteria harbored by the mouth. Their findings should shed light on the tooth decay process and ways to prevent it by the development of inhibitors to specific proteins generated by oral bacteria. Similar work is being done by an intramural researcher in the Laboratory of Microbiology and Immunology in collaboration with investigators at Transgene in Strasbourg, France; Ruhr University in Bochum, FRG; NIZO (a Dutch dairy research institute) in Ede, Netherlands; and at TNO (a Dutch biotechnology organization) in Leden, Netherlands.

Another intramural researcher in the Laboratory is collaborating with investigators at the Institute of Hygiene and Medical Microbiology in Heidelberg, FRG. He is studying a growth factor, called tumor necrosis factor, that spurs a type of immune response in the body.

Over the past fiscal year, the Laboratory of Oral Medicine has hosted several Visiting Fellows, Associates, or Scientists from Australia, Canada, China, India, Italy, Japan, United Kingdom, and U.S.S.R. Most of these investigators are studying the role of viruses in such autoimmune diseases as diabetes mellitus, Graves' disease, rheumatoid arthritis, and Lake Tahoe Syndrome. In related work, a Japanese Visiting Associate is trying to develop human monoclonal antibodies that might have therapeutic and diagnostic relevance.

Work by Visiting Scientists, Associates, and Fellows in the Laboratory of Developmental Biology and Anomalies has led to exciting findings on a protein that may be used to prevent paralysis from occurring after injury to the spinal cord. A Japanese Visiting Scientist has synthesized a protein that mimics one found naturally in the basement membrane, which lines all blood vessels and surrounds the nerves, muscles, and many of the organs in the body. Experiments reveal that this protein can prevent scarring and foster nerve regeneration.

Again this fiscal year, the Laboratory of Developmental Biology and Anomalies has exchanged staff with the Max Planck Institute for Biochemistry in Martinsreid, FRG, in the area of connective tissue research. This effort has expanded the training of both individuals and their groups and has led to a variety of collaborative studies. Particularly fruitful have been joint studies on basement membranes, which have clarified the structure of these important matrices. These informal collaborations have continued for approximately 20 years, allowing better division of responsibility and reduction of duplication.

Epidemiology and Oral Disease Prevention Program: A Finnish Visiting Scientist and expert in prevention of gum disease from the Periodontology De-

partment of the University of Helsinki completed a 2-year clinical trial to test a self-assessment system of bleeding gums designed to make young adults more aware of gum disease and ways to prevent it. Investigators in the Epidemiology and Oral Disease Prevention Program will be able to use the protocol developed for the study as a model when launching similar clinical trials of periodontal disease preventives.

Another Visiting Scientist with the Epidemiology and Oral Disease Prevention Program was a former Minister of Health and Social Affairs in Norway. In his studies, he compared Norway's dental delivery system to that of the United States and evaluated which factors were most important in preventing tooth decay. He also gave several presentations on the Norwegian health delivery system to NIDR staff and lectured to faculty at dental schools and schools of public health throughout the country.

A Danish expert in oral cancer, mucosal diseases, and associated epidemiology from the Royal Dental College of Copenhagen continued to assist in the development of research protocols for studies of oral mucosal lesions and oral conditions related to AIDS.

The director of the Department of Preventive Dentistry of Beijing Medical University in China completed a 6-month assignment with the Epidemiology and Oral Disease Prevention Program, where she received training and general orientation to the program's epidemiology methods and clinical trial procedures. The Chinese scientist, supported by UNICEF, intends to apply these methods to studies of oral disease in her homeland.

Chapter XI
National Institute of Diabetes and Digestive and Kidney Diseases

Introduction

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has a broad range of research interests, both basic and clinical, related to the spectrum of chronic, disabling diseases for which it has research responsibilities. Major areas of clinical research interest include diabetes, endocrinology, metabolic diseases, digestive diseases, nutrition, kidney and urologic diseases, and hematologic diseases. NIDDK places great emphasis on basic research related to these diseases, such as molecular biology, biochemistry, biophysics, physics, physical biology, chemistry, pathology, immunology, pathophysiology, metabolism, physiology, biology, pharmacology, and mathematics. The Institute conducts research to elucidate the underlying mechanisms of the diseases under its purview to facilitate development of treatments and means to prevent or arrest these diseases. NIDDK achieves these goals through a large intramural program that conducts basic and clinical research and through an extramural program that supports primarily investigator-initiated research grants, but also clinical trials and contracts. Some of NIDDK's international collaborations date back to the early days of the Institute. For example, the first participants in the NIH Visiting Program from Japan were invited to the NIH 30 years ago by the Chief, Laboratory of Chemistry. As further evidence of this international scientific cooperation, the NIH Alumni Association in Japan was recently founded in connection with the NIH Centennial.

Highlights of Recent Scientific Advances Resulting From International Activities

Advances in many aspects of molecular biology, in epidemiology and fundamental research in diabetes mellitus, and in pharmacology are significant among the many accomplishments of both the intramural and extramural program grantees' international activities.

Several epidemiologic studies of diabetes mellitus have produced data that elucidate aspects of incidence, prevalence, complications, and associated factors. A study comparing second-generation Japanese-Americans in the United States with U.S. Caucasians and native Japanese in Japan has shown that the U.S. Japanese have a higher prevalence of impaired glucose tolerance (IGT) and of noninsulin-dependent diabetes mellitus (NIDDM) than do the other two comparable groups. There is also a high associated prevalence of ischemic heart disease in the U.S. Japanese. These results suggest an inherent predisposition to IGT and arteriosclerotic heart disease that is affected by environmental variables such as diet, health habits, psychosocial stress, cultural factors, and lifestyle, as well as age, adiposity, patterns of body fat, glycemia, plasma lipids, and hormone levels.

An Australian grantee who has been studying diabetes mellitus in South Pacific populations has noted its emergence as a major chronic disease in association with rapid social, economic, lifestyle, and environmental changes and a marked difference in susceptibility in different populations. This grantee is searching for the major gene that determines diabetes mellitus.

The Phoenix Epidemiology and Clinical Research Branch and a group at Lund University, Sweden, have found postload glucose to be a significant predictor of mortality in a 20-year followup study of the relationship of IGT to the incidence of diabetes mellitus and death in Malmohus County.

Two grants funding research to identify genes for specific serious chronic diseases have been partially

successful. Using linkage analysis, a group in Oxford, England, has found the locus for adult polycystic kidney disease (APKD) on the short arm of chromosome 16. APKD is the cause of about 10 percent of end-stage renal disease. U.S., Canadian, and British scientists who are studying cystic fibrosis have narrowed the location of the cystic fibrosis gene to the middle third of the long arm of chromosome 7, a region of about a million DNA base pairs. In affected families, this makes it possible to predict children who also will be affected with cystic fibrosis, but it is not specific enough for diagnosis of asymptomatic carriers in the general population. In the United States, about 1 in 20 persons is a carrier of cystic fibrosis, and about 1 in 2,000 newborns has cystic fibrosis.

A novel antimalarial compound, arteether, has been developed from a natural Chinese product, qinghaosu, and is now being manufactured on a large scale by a procedure developed at NIDDK. Arteether will be mass-produced in China. This U.S.-China collaboration has developed analytic methods that will be used in studies in experimental animals and in humans to measure small quantities of primary metabolites. Another compound developed from a naturally occurring colchicine, 3-demethylthiocolchicine, has been prepared in an Israeli-NIH collaboration. This compound may be a replacement for colchicine, and its therapeutic properties will be tested in experimental amyloidosis, a disease that currently has no specific therapy.

Among other exciting advances in molecular biology and genetics, scientists in the Molecular Pathophysiology Branch, in collaboration with Scottish investigators, showed that a key binding (guanosine 5-triphosphate) regulatory protein was deficient in the livers of diabetic animals. These same NIH investigators, working with a scientist in Heidelberg, identified a novel GTP-binding membrane protein that they purified from neutrophils, which they found to be critical for the normal process of phagocytosis. In studies of the intracellular polymerization of sickle-cell hemoglobin, Laboratory of Chemical Biology scientists, working with British hematologists, found that small amounts of polymer can decrease marked red cell deformability. Danish grantees have characterized antibodies against pancreatic beta cells produced in patients who develop insulin-dependent diabetes mellitus (IDDM), and they have found specific targets for the antibodies on the beta cell surface.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

NIDDK participates in a bilateral agreement with Japan, has several different group endeavors with the World Health Organization (WHO), and engages in a number of cooperative research programs with specific foreign institutions in other countries, including the South Pacific Commission, China, Finland, India, Israel, Spain, Sweden, United Kingdom, Yugoslavia, and Taiwan. NIDDK provides support for U.S. scientists to work abroad in collaboration with leading investigators in their fields and for NIDDK scientists to travel to work with foreign collaborators as appropriate.

India: A collaborative study on urolithiasis, to be supported under the P.L. 480 Agreement, was ready for implementation by February 1987. The Director-General, Indian Council of Medical Research (ICMR), New Delhi, served as principal investigator, with project collaborators under the aegis of the Division of Kidney, Urology, and Hematology. The ICMR Deputy Director General met with the NIDDK staff in Bethesda, Maryland, in June 1987. Arrangements are progressing for a planning visit of NIDDK staff and consultants to India so that this study can be initiated. The study will assess the epidemiology of upper and lower urinary tract stones (kidney and bladder stones) to establish incidence and prevalence data for India. Co-investigators come from:

- ICMR (the Senior Deputy Director General, and the Director, Institute of Research in Medical Statistics);
- The All India Institute of Medical Sciences, New Delhi (Departments of Urology, Nephrology, and Medicine);
- The S.M.S. Medical College, Jaipur (Department of Urology);
- Osmania Medical College, Hyderabad (Department of Urology);
- Jawahar Lal Institute of Medical Education and Research;
- Pondicherry (Department of Urology); and
- A "low-prevalence area."

This study addresses the problem of bladder stones (lower urinary tract urolithiasis), which has caused serious discomfort for afflicted patients for at least five millennia. As European and North American

countries have become more industrialized, the pattern of urinary tract stone formation has shifted to upper tract stones, kidney predominantly. Bladder stones are still a significant problem in Southeast Asia, the Middle East, and parts of North Africa. There has been no careful study of why, as countries become more developed, a shift occurs from lower to upper urinary tract stones. Changes in nutrition are thought to figure prominently but have not been delineated. Dietary, metabolic, and physiologic studies as well as epidemiologic studies will be of significance not only in understanding bladder stones, but in elucidating the cause of the shift to kidney stones. These results will make a valuable contribution to knowledge in this field before the pattern of the bladder stone problem shifts. The goals of the study are:

- To elucidate differences between upper and lower urinary stones with respect to environmental and nutritional influences, physiologic background, and stone composition;
- To compare the type and frequency of different metabolic derangements (hypercalciuria, hyperoxaluria, primary hyperparathyroidism, renal tubular acidosis, cystinuria) in India and the United States;
- To correlate stone composition and morphologic appearance with the metabolic and endocrine profile and with nutritional and dietary influences; and
- To provide a more logical preventive and therapeutic treatment program for patients who suffer from urolithiasis.

Epidemiologic studies will include hospital questionnaires, hospital record studies, and data obtained prospectively by personal interviews and diet reviews. Dietary analyses will include assessment of fluid intake and water content of food, and dietary amounts of calcium, phosphorus, magnesium, and sodium. Patients will be selected randomly from the centers for pathophysiologic studies to include a search for metabolic derangements and infection with urea-splitting organisms. Urinary calculi passed spontaneously or surgically removed will be analyzed for crystalline configuration, epitaxy, and matrix components.

Israel: Cooperation with the U.S.-Israel Binational Science Foundation continues, and NIDDK provides consultants to review research proposals submitted under this agreement. Under this program, both an investigator in the Mathematical Research Branch, NIDDK, and one in the Department of Neurobiology, Hebrew University, Jerusalem, have developed mathematical models for understanding the role of excitable dendritic spines in neuronal integration. This collaboration developed during the Israeli investigator's tenure as an NIH Visiting Fellow.

Also supported by a grant from this foundation is a collaborative study between the Chief, Metabolic Diseases Branch, Beilinson Medical Center, Peta Tikva, Israel, and the Mineral Metabolism Section, Metabolic Diseases Branch, of human mononuclear cells as a target for 1,25-dihydroxyvitamin D. These investigators presented work stemming from this collaboration at the Ninth International Conference on Calcium Regulating Hormones and Bone Metabolism, in Nice, France, in October 1986.

Italy: The U.S.-Italy Science and Technology Agreement, signed in 1984, made formal the bilateral cooperation in the fields of diabetes and metabolic diseases that had been conducted informally for 10 years, with the addition of metabolic diseases. When this agreement was renegotiated, the San Raffaele Institute in Milan was added. NIDDK involvement with this group includes investigators from the Phoenix Epidemiology and Clinical Research Branch, the Diabetes Control and Complications Trial, and the intramural program.

In concert with the U.S.-Italy Collaborative Agreement for Research in Metabolic Diseases, the Scientific Officer of the Diabetes Control and Complications Trial visited Italy in March 1987 and continued his consultation with several Italian research groups involved in clinical trials. With funding from the Italian Government's National Research Council, the Chief, Laboratory of Chemical Physics, is collaborating with an investigator at the University of Parma, Italy, on studies of equilibrium oxygen binding to hemoglobin in single crystals. Another NIDDK investigator, on a 2-month visit to the University of Parma, studied the photoreduction of flavins and flavocytochrome B2, also funded by the Italian National Research Council and the Italian Ministry of Public Education.

Japan: The U.S.-Japan Malnutrition Panel, a binational steering committee of experts, was established in 1966 as part of the U.S.-Japan Cooperative Medical Sciences Program. Although the overall U.S.-Japan Cooperative Medical Sciences Program is administered by the National Institute of Allergy and Infectious Diseases, the malnutrition portion is the responsibility of the Division of Digestive Diseases and Nutrition, NIDDK.

The original purpose of the Malnutrition Panel was to conduct research that could be applied to help alleviate malnutrition, especially in Southeast Asia. Malnutrition continues to be a serious problem in most Asian countries, where protein-calorie malnutrition and deficiencies of iron and vitamin A are the most common forms. Alternately, as Japan has become more affluent (its gross national product is third highest in the world) and the Japanese diet has become more westernized, there has been a change in nutritional status and in nutritionally related diseases, such as obesity and diabetes.

During the past year, there have been several developments of substantial importance to the Joint U.S.-Japan Malnutrition Panels. These activities include:

- The conclusion of the pentennial program review of the Joint U.S.-Japan Malnutrition Panels;
- Two joint panel meetings with accompanying symposia held (Osaka, fall 1986; San Diego, spring 1987); and
- Implementation of four new research priority goals that emphasize increased U.S. and Japan research collaboration.

With reorientation of research priorities and new plans to stimulate and foster collaborative research, the Joint Subcommittee on Program Review and Planning recommended that the Malnutrition Panel be continued. Efforts have proceeded vigorously to use various support mechanisms to achieve these new goals, with emphasis on three research priorities:

- Nutritional aspects of bone disease, including interrelationships of osteoporosis, calcium, and influences of other nutrients and the aging process;
- Nutritional significance of unsaturated fatty acids in health and disease; and
- Endogenous mediators of inflammation, infection, and malignancy and their effects on nutritional metabolism.

Nutritional assessment was emphasized in the Osaka workshop, September 28–30, 1987. At the end of the International Symposium on Clinical Nutrition in San Diego, April 27–29, 1987, the Joint U.S.-Japan Malnutrition Panels sponsored a symposium entitled "Dietary Guidelines: International and National Perspectives" at which nutritional experts from around the world presented papers. Emphasis will be on the fatty acid area in the symposium and panel meeting to be held in Tokyo, Japan, in September 1988.

The new priorities for the U.S.-Japan Malnutrition Panel have led to increased focus on the nutritional concerns of the United States and Japan, particularly the health consequences of changing dietary patterns and food habits. Dietary patterns continue to be recognized as a contributing variable or risk factor in a number of chronic diseases. The gradual westernization of the Japanese diet has provided an opportunity to study the relationship of dietary components to chronic disease through basic, clinical, and epidemiologic research in both countries. Innovative measures of nutritional assessment may improve data collection.

Highlights of the investigations supported in association with the Malnutrition Panel of the U.S.-Japan Cooperative Medical Sciences Program follow.

Studies of a second-generation community of Japanese-Americans living in the United States who have a high prevalence of IGT and NIDDM: The prevalence rates are higher than those observed in comparable U.S. Caucasians or native Japanese in Japan with an associated high prevalence of ischemic heart disease. The data suggest an inherent tendency to develop abnormal glucose tolerance and atherosclerotic disease that is affected by environmental variables. These variables include diet, health habits, psychosocial stress, and cultural factors, as well as age, adiposity, pattern of body fat, glycemia, plasma lipids, hormone levels, and lifestyle. These studies require the availability of racially homogeneous and chronologically discrete age groups within the Japanese-American population, long exposure to western lifestyle, current middle-class socioeconomic status, population stability, and other environmental conditions relevant to the larger U.S. population.

A study of the possible relationships between diet and lifestyle factors and the bone status of premenopausal and postmenopausal Japanese women: Data are being collected on levels of physical activity, past dietary calcium intake, lactation length, weight, height, and current calcium intake. Preliminary data show a low mean intake of dietary calcium in both groups. The premenopausal group showed higher values for various measures of bone density than did the postmenopausal group, probably reflecting the effects of aging, hormonal changes, and possibly differences in nutriture during the growth period. A subgroup of postmenopausal women whose past dietary calcium intake was more than 600 mg/day had higher bone densities than did those women who consumed less than 600 mg/day of calcium.

Developmental work and evaluation of the applicability of a new method for measurement of stable zinc isotopes and biologic samples: This method uses a fast atom bombardment mass spectrometry technique to measure zinc stable isotopes in various

samples. It eliminates interference from other targets within the fast atom bombardment and provides definition and quantitation of other previously unrecognized isotope fractionation. The overall precision for measurement of stable zinc isotopes in fecal samples has been at the 1 percent level of enrichment and is within 1.5 percent relative standard deviation. This figure for precision covers the entire procedure from the dried fecal sample to the final fast atom bombardment mass spectrometry analysis.

Spain: Studies continue under the U.S.-Spain Joint Committee on Scientific and Technological Cooperation, and new ones have been reviewed for funding. The NIDDK collaborative study with the Endocrinology Division of the Hospital de la Santa Cruz y S, Barcelona, completed its third year of a 5-year grant for studies of insulin and embryogenesis. This cooperative effort has had major mutual benefits; for example, one Spanish Fellow has completed his Ph.D. thesis and is continuing research on this project; another is continuing studies on Type I insulin-like growth factor (IGF) localization in the chick embryo with U.S. support of supplies and technical advice. The Diabetes Branch, NIDDK, hosts a Fellow from Madrid and one from Barcelona on a study that focuses on the role of insulin and insulin-related peptides in normal and abnormal embryonic development. Specific studies include:

- Developmental regulation and characteristics of receptors for insulin and for IGFs during embryogenesis using the chick embryo as a model;
- Effects of insulin, insulin analogues, and IGFs on metabolic and growth parameters in early chick embryos;
- Consequences of neutralizing insulin action by applying insulin antibodies and insulin-receptor antibodies in human diabetic mothers;
- Molecular biologic aspects of mRNA for insulin and insulin receptors in chick embryo tissues; and
- Exploration of the effects of insulin on expression on nonhormonal genes in nonvertebrates using the sea urchin embryo as a model.

Accomplishments for 1987 include the discovery that IGF receptors are present in chick embryo brain, heart, limb buds, and liver and that insulin receptors and Type I IGF receptors are present in adult chick adipose tissue. Type II IGF receptors were absent in all tissues studied; IGF and, to a lesser extent, insulin receptors change in number during development in different tissues, and the apparent molecular weight of Type I IGF and of insulin receptors changes during differentiation and organogenesis. No patterns of anti-insulin antibodies have been discernible in human maternal serum in an 18-patient study of the relationship of the peptides IGF and insulin and anti-insulin antibodies to anthropometric parameters in newborn infants of diabetic mothers.

Activities With International and Multinational Organizations

European Molecular Biology Organization (EMBO): With support from a European Molecular Biology Organization grant, scientists in the Laboratory of Cellular and Developmental Biology continue to participate in a large collaborative study that includes European scientists from Imperial College, London, United Kingdom; University of York, United Kingdom; Plant Genetic Systems N.V., Ghent, Belgium; University of Brussels, Belgium; and Université Paris-Sud, France. This research involves studies of the structure of a bacterial extracellular ribonuclease and an intracellular inhibitor that form a one-to-one complex. Recently, the genes for both proteins have been cloned and expressed in different bacterial species. The potential for *in vitro* mutagenesis of these genes, and for study of the structure of proteins both individually and as a complex, offers significant opportunities for understanding the mechanisms of protein folding and protein-protein interaction.

International League Against Rheumatism: The Chief, Phoenix Branch, serves as a consultant and advisor to the International League Against Rheumatism Study of Prevalence of Rheumatoid Arthritis, Systemic Lupus Erythematosus, and Ankylosing Spondylitis in the Chinese Population, which is being undertaken with China. The first phase of the study entailed development of a questionnaire, followed by appropriate modification and refinement of this instrument. After the questionnaire was tested, 2,000 textile factory workers were interviewed, had joint examinations, and underwent serologic testing for rheumatoid factor and for antinuclear antibodies. On the basis of these data, protocol modifications were made, and the questionnaire was tested in a rural population close to Beijing. In 1988, the final protocol adopted will be applied to a random sample of the Chinese Han population. It is estimated that about 6,000 persons will participate in this study, which should lead to estimates of the prevalence of these diseases in the Chinese population.

Medical Research Council: The Steroid Reference Collection at Westfield College, London, England, is a research resource started in 1965. The collection has samples of approximately 5,000 steroids, most of which are not available commercially. The ref-

erence compounds are supplied worldwide to investigators interested in steroid endocrinology and metabolism. The samples are used as standards for chromatography, spectroscopy, and radioimmunoassay. The Medical Research Council and the NIH cooperatively have supported the collection, for which the NIDDK Endocrinology Program provides about 30 percent of the cost, and NIDDK receives a supply of steroids for distribution to U.S. scientists.

World Health Organization: NIDDK has a major involvement with WHO in diabetes mellitus, as well as several other agreements on a lesser scale. Through the WHO Collaborating Centers related to diabetes mellitus, NIDDK is involved with the Pan American Health Organization, the South Pacific Commission, and China.

Two WHO Collaborating Centers are involved with studies of diabetes mellitus: the WHO Collaborating Center for Diabetes Research, Information, and Education (DRIE), designated in April 1985 within the Division of Diabetes, Endocrinology, and Metabolism, and the WHO Collaborating Center for the Methodology, Design, and Analysis of Epidemiological and Clinical Research in Diabetes (MDAECRD), designated in May 1986, which is an activity of the Phoenix Epidemiology and Clinical Research Branch.

WHO Collaborating Center for Diabetes Research, Information, and Education: The functions of the DRIE Collaborating Center are:

- To encourage and solicit international research applications eligible for support through NIH research grants and contracts;
- To sponsor U.S. study periods for foreign investigators;
- To provide American consultant scientists to WHO member nations;
- To provide information and materials in response to inquiries in areas of diabetes research;
- To assist WHO in the development of an educational program for health professionals and diabetes patients by creation and distribution of special materials; and
- To serve in a consultant capacity to WHO and other international committees.

The center participates in an international effort sponsored by WHO to develop epidemiologic study capabilities in diabetes that include:

- Quantifying mortality;
- Developing guidelines for field studies;
- Preparing a document on the worldwide scope and impact of diabetes;
- Identifying and fostering opportunities for training in epidemiology; and
- Standardizing methodologies for assessment of diabetic complications.

These plans were delineated at a meeting of all WHO diabetes center directors (Lexington, Kentucky, June 1987).

The Collaborating Center serves as a provider of information about diabetes research. Through the National Diabetes Information Clearinghouse, it also distributes NIDDK publications, including *The Diabetes Dictionary* and *Diabetes in America*, internationally. The center works closely with the Diabetes Programs Branch in developing international research grants about diabetes and its complications, is sponsoring an epidemiology Fellow for short-term training in epidemiologic research methods and analysis of data sets, and hosts Visiting Scientists with research interests in diabetes, especially epidemiology.

WHO Collaborating Center for the Methodology, Design, and Analysis of Epidemiological and Clinical Research in Diabetes: The Phoenix Branch serves as one of the WHO Collaborating Centers for Diabetes, which is a network created to facilitate international training and research in diabetes. The purposes of MDAECRD are to collaborate with WHO in the implementation of the WHO International Diabetes Foundation action program and to provide advice, consultation, and collaboration with other investigators in the design, methodology, and analysis of epidemiologic and clinical investigations relating to the etiology and pathogenesis of NIDDM and its complications. The center assists in the development and application of standard methods for epidemiologic and clinical investigations and provides advice and methods of data analysis relating to diabetes. It undertakes to provide short- or long-term training experience for Fellows who wish to expand their knowledge in the methods and application of epidemiologic and clinical research in NIDDM.

The center focuses primarily on the epidemiology and complications of diabetes and clinical research related to insulin resistance and intracellular abnormalities associated with, or leading to, NIDDM. It provides:

- Consultation, advice, and collaboration in the application of field, clinical, and/or laboratory methods for diabetes investigations;

- Training opportunities and practical experience in such techniques;
- Advice and help in the design of new studies; and
- Assistance in establishing standard laboratory methods and their quality control, using duplicate analyses and sera exchanges.

The Phoenix Branch serves as a central laboratory for the followup examination aspects of the WHO Multinational Study of Vascular Disease in Diabetes, for which it provides analyses of serum and urine from several of the participating centers. As a participating center in this study, the Phoenix Branch has provided an 8-year followup of patients, completed one associated mortality study, and will conduct another mortality study. The Phoenix Branch also is collaborating with the China Friendship Hospital, Beijing, in an investigation of epidemiology and natural history of NIDDM and IGT. During the past year, 95,000 Chinese inhabitants of Daqing were screened, resulting in identification of 1,193 persons with NIDDM: 600 persons by glucose tolerance and 593 persons by IGT using WHO criteria. These groups will be followed prospectively, along with a control group matched for age and sex. The IGT group will be randomized into a controlled trial to determine whether the incidence of NIDDM can be reduced by intervention, with either diet and exercise or sulfonylurea. Although the protocol for this trial is not yet complete, the intervention trial is planned to continue for at least 5 years.

Epidemiologists from the Phoenix Branch are collaborating in the development of a field workers' guide in diabetic epidemiology, to be completed in 1988. The Director, Phoenix Branch, participated as a lecturer and tutor in a WHO Postgraduate Course on the public health aspects of diabetes mellitus in Cambridge, England, in June 1987.

The WHO MDAECRD continues to collaborate with the South Pacific Commission in analysis and publication of findings from the Pacific. In August 1987, the Commission conducted a followup of 1,200 participants in the 1980 Raretonga diabetes survey to determine the incidence of diabetes and of diabetes-related complications. Urine albumin/creatinine ratios are part of these followup analyses. Four publications have come from this study: *Glucose Tolerance in Polynesia: Population-based Surveys in Raretonga and Nieue; A Cross-sectional Analysis of Blood Pressure and Its Determinants in Eleven Pacific Populations; Smoking Rates in Pacific Islands; and Hypertension and Indicators of Coronary Artery Disease in Wallis Polynesians: An Urban-Rural Comparison.*

The Medicinal Chemistry Section, Laboratory of Analytical Chemistry, continues its collaboration with the WHO Scientific Working Group on Malaria Chemotherapy. The novel antimalarial drug arteether, produced under this program, is scheduled for clinical trials in 1988 and is being manufactured on a large scale by the procedure developed at the NIH. China will be responsible for mass production of the drug. FY 1987 research at NIDDK focused on arteether metabolism, and a series of putative metabolites was prepared. Analytic methods that allow detection of very small quantities of primary metabolites were developed in cooperation with scientists in the Department of Organic Chemistry, Beijing Institute of Pharmaceutics, China, and will be used in studies of this drug's fate, in both experimental animals and humans. The Chief, Laboratory of Molecular and Cellular Biology, continues to serve on the Parvovirus Study Group Coordinating Subcommittee of the WHO International Committee on Taxonomy of Viruses.

Extramural Programs

Division of Diabetes, Endocrinology, and Metabolism: In FY 1987, this Division supported 21 research grants and cooperative agreements in nine foreign countries.

Diabetes Program: The Diabetes Program supported 10 research projects and two cooperative agreements in six countries. Led by an investigator at the Royal Southern Memorial Hospital, Melbourne, Australia, a project to assess diabetes mellitus and IGT in South Pacific populations continues to be productive. The emergence of diabetes mellitus as a major chronic disease associated with rapid social, economic, lifestyle, and environmental changes is being examined. Marked differences in susceptibility to diabetes among various ethnic groups in this region of the world have been found and may apply to etiology of diabetes in specific U.S. subpopulations. Many of the studies are longitudinal, thus permitting investigation of the contributions of specific factors such as obesity, genetics, diet, and physical activity, to the etiology of this disease. A search for a gene that determines diabetes is under way. A successful outcome would provide a major breakthrough in diabetes research by quantifying the genetic component contributing to the etiology of diabetes mellitus and by identifying people at genetic risk of developing this disease for further studies.

A Canadian scientist at the University of Toronto is being supported to evaluate an implantable, controlled-release micropump that can deliver insulin at variable rates. A prototype of this pump has been

implanted in diabetic dogs and has been functional for more than 6 months. The controlled-release micropump may offer a means to restore normoglycemia to diabetic patients so that the degenerative complications of diabetes can be prevented.

Canadian investigators at McGill University in Montreal are studying the multifaceted hormone somatostatin, which is produced in many tissues including pancreatic islets, and appears to play an important role in the control of secretion of several other hormones, including insulin. Scientists have elucidated a great deal about the biosynthesis, metabolism, and mechanism of action of somatostatin, including that somatostatin appears in various molecular forms and is secreted in excess in an animal model of diabetes. Another research project at McGill is directed to the basic mechanism of insulin action in cells. Once insulin binds to insulin receptors on the cell surface, this insulin-insulin receptor complex is taken into the cell in specialized compartments called endosomes. One of the early actions of insulin is to increase a certain "kinase" activity in the cell. These investigators have shown that this kinase activity is concentrated and augmented in the endosomes, suggesting that the endosome may be an important area of insulin action.

Under cooperative agreements, two Canadian scientists (University of Toronto, University of Western Ontario) are participating in the Diabetes Control and Complications Trial, a multicenter-controlled clinical trial that has been designed to assess the relationship between metabolic control and early vascular complications of insulin-dependent diabetes mellitus. After successfully completing a feasibility study, the trial is currently recruiting and randomizing additional volunteers for the full-scale clinical trial. It is anticipated that a total of 1,400 patients will be studied at 27 centers over the next 5 years.

A Chinese scientist in the Institute of Biophysics, Beijing, is investigating the mechanism of interaction of the two separate chains of insulin leading to their correct pairing. These studies should provide important information about how insulin is folded during its biosynthesis in the body.

Danish scientists at the Nordic Insulin Laboratory, Gentofe, have continued their highly productive studies on the nature of the autoimmune process that leads to IDDM. Most recently, they have been characterizing the antibodies against pancreatic beta cells produced in patients who develop IDDM and exploring antibody interference with the function of beta cells. In addition, they have identified specific targets for the antibodies on the beta cell surface. These findings have increased understanding of the underlying causes of IDDM and will be important for the rational development of new potentially curative or preventive therapies.

Finnish studies conducted at the University of Helsinki should complement ongoing U.S. studies about the etiology and epidemiology of IDDM. Finland has the highest recorded rate of IDDM in the world, and a central drug registry has facilitated complete identification of all IDDM patients in Finland. This registry will be used to compare the characteristics of IDDM patients in Finland with those of U.S. patients. Further, a prospective registry of new-onset cases of IDDM will be used to investigate the roles of genetics and environment in the etiology of IDDM and to compare these data to those obtained in the United States. A nationwide registry of pregnancies will be used to assess whether *in utero* exposures to viral infections or environmental factors contribute to the pathogenesis of IDDM.

Research supported at the University of Oxford, England, is determining the effect of different types of diabetes therapy and different degrees of diabetic control on the development of diabetic microvascular disease. In particular, plasma and urine biochemical variables thought to be associated with microvascular disease are being measured to determine prospectively whether any relationship exists with the subsequent development of kidney disease. This study is part of the larger, randomized clinical trial of treatment of people with NIDDM, known as the "U.K. Prospective Study of Therapies of Maturity Onset Diabetes."

A University of London investigator is examining the relationship between the time when a person experiences a stressful life event and the appearance of immunologic markers for IDDM. Families in which a member has developed either diabetes mellitus or islet cell antibodies characteristic of a prediabetic state are being identified. These families are evaluated not only for biologic components of their IDDM but also for data concerning life events and difficulties.

Led by investigators at the University of Pittsburgh, scientists in Pennsylvania, Finland, Israel, and Japan are investigating the rates and causes of mortality from IDDM for more than 9,000 patients in population-based cohorts in their respective countries. For the first time, standard definitions of diabetes and causes of death are being employed internationally. Through this study, the specific impact of clinical, racial and ethnic, and lifestyle and environmental contributions to diabetes mortality will be assessed.

The Diabetes Program supports two research resource contracts that provide animals and human tissues for study by investigators in the United States and around the world. One is at the University of Massachusetts, which maintains a colony of diabetes-prone BB rats that are an invaluable model for the study of IDDM. The other contract is for the National Disease Research Interchange, an organization that procures human tissue from cadavers of diabetic and nondiabetic individuals for use in studies of diabetes by biomedical research workers throughout the world.

Endocrinology Program: The Endocrinology Program supports five research projects in five countries, as well as one major research contract of international importance. At the University of Brussels, Belgium, investigators are studying thyroglobulin, the large protein that serves as a storage form of thyroid hormone in the thyroid gland. Previous work by this group has elucidated characteristics of the thyroglobulin molecule, which may explain why Graves' disease, an autoimmune disease of the thyroid, may also cause Graves' ophthalmopathy, an eye disease that occurs frequently in association with thyroid dysfunction. Further, these investigators propose to show how thyroglobulin gene transcription is regulated by thyrotropin and cyclic AMP (adenosine 3',5'-cyclic monophosphate). They also will undertake evolutionary studies using thyroglobulin gene products from birds, reptiles, and fish, which they will compare to beef thyroglobulin gene products to see if there are detectable patterns to explain the evolution of the mammalian thyroglobulin molecule, which is larger and more complex than that of lower forms. Finally, studies will be performed that will attempt to determine which portions of the thyroglobulin molecules are responsible for the development of thyroid autoimmune diseases.

At McGill University, Montreal, Canada, a grantee is studying the mechanism by which alpha-2-μ-globulin, a glycoprotein produced by the liver, regulates the production of hormones from the anterior pituitary gland. Previous work has shown that alpha-2-μ-globulin production is stimulated by androgens, glucocorticoids, and thyroid hormone, all of which are produced in glands that are in turn stimulated by tropic hormones from the anterior pituitary (gonadotropin, adrenocorticotropin, and thyroid-stimulating hormone). The androgens, glycocorticoids, and thyroid hormone act back on the pituitary to decrease their own production in a negative-feedback arrangement. The investigator has demonstrated that anterior pituitary cells in culture have receptors for the alpha-2-μ-globulin. Furthermore, the cultured cells showing these receptors are cells that produce the hormones previously shown to be affected by alpha-2-μ-globulin, namely somatotrophs, mammotrophs, and gonadotrophs. In addition, experiments showed that pituitary cells preincubated with growth hormone-inhibiting factor (GIF) or growth hormone-stimulating factor (GRF) had changed the affinity of these cells for alpha-2-μ-globulin. GIF and GRF are hormones normally produced in the hypothalamus.

An investigator at the Hebrew University, Jerusalem, Israel, is studying the effect of 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), a calcium-regulating hormone. Recently, this hormone has been shown to modulate the body's immune system and the growth of leukemia cell lines in humans and mice. One of this hormone's effects on the immune system is the regulation of mononuclear phagocytic cells (macrophages) that fight invading organisms by engulfing them. These cells also appear to regulate the body's immune response by processing antigens and then releasing cellular factors, which modulate the activities of lymphocytes. The cells may be an anticancer defense mechanism by inhibiting growth of cancerous cells and killing them. Finally, macrophages are now believed to be modulators of bone metabolism by releasing bone resorption factors. The investigator is studying the mechanism of action of $1,25(OH)_2D_3$ on those immune cells by:

- Determining if macrophages obtained from vitamin D-deficient animals show decreased tumoricidal activity, and if vitamin D3 can correct the defect;
- Studying changes in vitamin D3 receptors in macrophages with vitamin D deficiency in order to correlate enhanced tumoricidal activity with receptor numbers; and
- Studying the possibility that there is an interaction of $1,25(OH)_2D_3$ with a cellular growth factor that causes differentiation of these cells into immune cells.

An investigator at the Catholic University, Nijmegen, Netherlands, is studying the genes of the toad *Xenopus laevis*. In Xenopus, two propriomelanocortin (POMC) genes exist, both of which are expressed in the pituitary. The genes express the POMC, from which several hormones are derived, including alpha-melanophore-stimulating hormone. The toad has a large intermediate pituitary lobe where POMC is made, and the pathways and factors that regulate POMC gene expression are well understood. The toad's large eggs can be used in gene transplant studies. Various genetic studies are under way to determine which areas of the genes produce active hor-

mone and which areas are important to gene expression. In later studies, gene mutations will be induced, and the mutated Xenopus POMC genes will be injected into fertilized Xenopus eggs. Developing toads will be used to determine how mutations affect the POMC hormone, its expression, and its products.

An investigator at Lincoln College, Canterbury, New Zealand, has developed a method for determining production rates of pituitary hormones under various conditions. Catheters are inserted into blood vessels draining the pituitary gland of horses; then the conscious, unrestrained horses are used for studies of pituitary hormones produced under varying hormonal and physiologic conditions. These large animals can be studied for at least a week, even though frequent blood samples are taken from the pituitary venous sinus. This technique should allow greater precision in measurement of pituitary hormone release.

The National Hormone and Pituitary Program, an important research resource provided to the scientific community, extracts and distributes highly purified hormones and antisera to these hormones to qualified investigators in this country and abroad. The hormones produced are used in laboratory research and also serve as standards. Approximately 5,000 samples are distributed annually. Up to one-third of the requests come from scientists in foreign countries, including the United Kingdom, most European countries, Scandinavia, Australia, South America, India, and China.

Metabolic Diseases Research Program: The Metabolic Diseases Research Program supported four research projects in three countries in FY 1987.

A group of Belgian scientists at the Catholic University of Louvain are unraveling the mechanisms of inborn errors of carbohydrate and lipid metabolism and of storage diseases. Their research also involves studies of the major regulatory sugar molecule, the fructose 2,6-diphosphate.

A group of Canadian scientists at the University of British Columbia are studying blood proteins and enzymes to determine the mechanism of oxygen storage, transport, and activation by various biophysical methods such as electrochemical, kinetic, optical, and magnetic resonance techniques.

Two groups of Israeli scientists are supported by this program. The group at the Technion-Israel Institute of Technology, Haifa, is studying the mechanism of intracellular protein breakdown and the role of the ubiquitin conjugation pathway in this process. Ubiquitin is a small heat-stable polypeptide that binds to proteins and appears to initiate the proteins' breakdown. Since this happens in the presence of adenosine triphosphate (ATP), a basic constituent of the living cell, the research group is trying to understand the mechanism by which the proteins, ubiquitin, and ATP interact to initiate breakdown of intracellular proteins. The second group of scientists at the Hebrew University of Jerusalem is studying a neurotransmitter-receptor system and the way in which it interacts with the adenylate cyclase, or "second messenger" membrane signaling system.

Cystic Fibrosis Program: Through the research of investigators in the United States, Canada, and United Kingdom, the location of the cystic fibrosis gene has been narrowed to the middle third of the long arm of chromosome 7 in a region of about a million DNA base pairs. Using genetic analyses, these investigators examined DNA samples from families having children with cystic fibrosis and discovered they could predict which children were affected with the disease. Although the new marker for the cystic fibrosis gene allows detection of the gene in DNA samples from members of families where there is a known case of cystic fibrosis, it is not specific enough to diagnose asymptomatic carriers in the general population. However, the finding of markers closely linked to the cystic fibrosis gene brings the actual isolation of the gene itself much closer. The NIDDK Cystic Fibrosis Program supports the research efforts of the Canadian research group at the Hospital for Sick Children, Toronto.

Division of Kidney, Urologic, and Hematologic Diseases: Mapping of the adult polycystic kidney disease gene mutation is the topic for a research grant supported at the John Radcliffe Infirmary, University of Oxford, England. This grantee, who has done preliminary studies using linkage analysis indicating that the APKD locus is on the short arm of chromosome 16, is defining the genetic heterogeneity in APKD and will construct a linkage map of chromosome 16 using polymorphic probes isolated from chromosome 16 libraries. It is hoped that the APKD gene can be isolated, thus contributing to understanding of the molecular pathology of this disease, which is responsible for about 10 percent of end-stage renal disease.

International Conferences, Meetings, and Seminars

Considerable international activity in the diabetes field continues. The Director, National Diabetes Data Group, consulted with the WHO Collaborating Center, Melbourne, Australia, for 3 weeks in 1987 and made presentations on the epidemiology and public health aspects of diabetes mellitus in United States and South Pacific data sets, especially as related to

the role of IGT in etiology and as a risk factor for complications. The Director of the WHO/Diabetes Endocrinology Metabolism Division Collaborating Center attended the meeting of WHO Collaborating Centers held in Lexington, Kentucky, in June 1987, at which summaries of programs were presented and working groups developed recommendations for an International WHO Action Plan on Diabetes Mellitus. The Diabetes Control and Complications Trial Science Officer discussed the trial's progress at the Fourth Milano International Meeting on Diabetes, Milan, Italy, March 1987. The Diabetes Research Program Director attended an international conference on insulin action and diabetes, held in Calgary, Alberta, Canada, March 1987.

NIDDK provided support for a number of international conferences, workshops, and symposia, for example, a Division of Kidney, Urologic, and Hematologic Diseases conference grant for the Eighth International Conference on Proteins of Iron Transport and Storage, held in Montreal, Canada, May 1987. The Diabetes Program supported a genetic analysis workshop, held in conjunction with the Ninth International Workshop on Human Gene Mapping (for which travel support for U.S. scientists was provided by the Metabolic Diseases Program), Paris, France, September 1987. The Division of Diabetes, Endocrinology, and Metabolism also supported two cystic fibrosis meetings: the Sixth Professional Conference "Broken Arrow," Kimberly, Ontario, November 1986, at which scientists and clinicians conferred about molecular aspects of cystic fibrosis; and the International Conference on Cellular and Molecular Basis of Cystic Fibrosis, Verona, Italy, June 1987, at which recent advances in genetics, electrolyte transport, secretion and secretory products, membrane mechanisms, and intracellular regulation were featured.

The Metabolic Diseases Research Program Director attended the Fourth International Congress of Inborn Errors of Metabolism, Sendai, Japan, May 1987, and was involved in its planning. This program provided travel support for U.S. scientists to attend a conference on crystal growth of biological molecules, which addressed problems of macromolecular crystallization and was held in Bichenberg, France, July 1987. The Metabolic Diseases Research Program also cosponsored the International Conference on Experimental and Theoretical Analysis of Metabolic Processes, which was held in Bigfork, Montana, September 1987. The conference focused on:

- The current state of metabolic modeling;
- The fate of glucose load;
- Gluconeogenesis;
- Glucokinetics;
- Insulin metabolism in humans and animals;
- Metabolic models using enzyme data; and,
- Theoretical aspects of metabolic control.

Intramural Programs and Activities

The intramural program fosters collaboration with scientists and laboratories throughout the world and provides consultation, advice, materials, procedures, and analyses to universities, research institutions, investigators, and laboratories worldwide. NIDDK intramural scientists have more than 40 individual cooperative research efforts with scientists from at least 15 countries. In FY 1987, the Institute had 205 Visiting Scientists, Associates, Fellows, and Guest Researchers from 38 different countries. Although numbers fluctuated during the year, in September 1987 the greatest number of foreign nationals came from: Japan (35); China and Italy (17 each); Israel (16); India (12); and United Kingdom (10). There were up to 12 East European nationals in the intramural program, who came from: Czechoslovakia (1), Hungary (2), Poland (6), Romania (1), and Yugoslavia (2). Fifteen intramural scientists came from Latin American countries: Argentina (3); Brazil (5); Chile (4); Mexico (2); and Peru (1).

Phoenix Epidemiology and Clinical Research Branch: The Chief, Diabetes and Arthritis Epidemiology Section, Phoenix Branch, is chairman of the steering committee for a multicenter study investigating the effects of intervention on impaired glucose tolerance. Other centers committed to or interested in the study include: Cardiff, Wales; Dalby, Sweden; Helsinki, Finland; Malmö, Sweden; and Newcastle on Tyne, England. A randomized clinical trial among adults with IGT will be undertaken to determine if the development of NIDDM and related cardiovascular disease can be delayed or prevented. Plans include randomly allocating patients to sulfonylurea or placebo groups and to standard or special diet and exercise treatment using a factorial design for the 400–600 subjects to be recruited. Partial support has been obtained from the Swedish Medical Research Council and from Lund University, Sweden.

The same section, in collaboration with Lund University, Sweden, has completed a 20-year followup of IGT, including incidence of diabetes and of death in Malmohus County, Sweden. It was found that postload glucose concentration was a very significant predictor of mortality.

The Diabetes and Arthritis Epidemiology Section, in collaboration with the Karolinska Institute, Stockholm, Sweden, also is continuing a study of insulin concentrations in cord bloods of diabetic and nondiabetic Pima Indian infants. The relationship between concentrations of fetal glycosylated hemoglobin, C-peptide, pro-insulin, and insulin in cord blood and maternal glycosylated hemoglobin and glucose concentrations in the third trimester of pregnancy will be studied. Analyses will be done in Stockholm and compared with samples collected and assayed in the same laboratory in Stockholm.

The Clinical Diabetes and Nutrition Section continues a collaboration on two studies with the San Raffaele Institute, Milan, Italy. One study involves measurement of lipoprotein composition and VLDL metabolism in Type 1 diabetics after conventional insulin therapy or after implantation of an intraperitoneal device for insulin delivery. The second study investigates the biodistribution of low-density lipoproteins in humans using technetium-labeled LDL and the gamma camera. In addition, the two units are involved in a collaborative study involving identification of isoforms of human apolipoprotein B. The relative prevalences of the various isoforms in the Pima population are compared to those of Caucasians, and samples from Pima families are used to determine whether there is a correlation between the isoforms and plasma LDL concentrations. This section has collaborated with a group in the Second Department of Medicine, Helsinki, Finland, on studies of the interaction between sex hormone lipase activities and HDL concentrations and obesity.

Laboratory of Bio-Organic Chemistry: The Laboratory of Bio-Organic Chemistry has collaborations with nine overseas groups. Four of these efforts are involved with biologically active substances from amphibians in cooperation with the University of Melbourne, Australia; an investigator in Ecuador; University of Rome, Italy; and Osaka City University, Japan. Immunocytochemical studies on catechol-O-methyltransferase are being conducted with investigators at Okayama and Nagoya Universities, Japan. Other research collaborations include studies of:

- Metabolism of benzacridines with scientists at the University of Sydney, Australia;
- Development of photoaffinity labels for receptors and ion channels at Hokkaido University, Japan; and
- Synthesis of optimally active arene oxides involved in hepatic metabolism at Queens University of Belfast, Northern Ireland.

Laboratory of Biochemical Pharmacology: The Section on Pharmacology continues studies on the optical properties of crystals of tryptophan synthase and its substrates with investigators at a laboratory of the University of Parma, Italy, which has a microspectrophotometer especially designed for this type of study. This same group is examining the effects of site-specific mutagenesis of tryptophan synthase on the enzyme mechanism with scientists at the Protein Institute, Osaka University, Japan.

Clinical Endocrinology Branch: The Chief, Clinical Endocrinology Branch, continues collaborative efforts with Italian scientists that extend back over three decades. Based at the University of Rome for a work-study visit, he conferred with a group at the Thyroid Center, II Clinica Medica, as well as with former Visiting Fellows at the Universities of Pisa, Messina, and Catania, Italy.

Laboratory of Biochemistry and Metabolism: The Chief, Cell Regulation Section, is collaborating with a number of groups at the University of Naples, Italy, on continuing studies of the regulation of thyroglobulin gene transcription by insulin and Type I IGF and the destruction of tyrosine kinase in thyroglobulin preparations. Joint studies with two other Italian institutions are of autoantibodies in Graves' disease, with two investigators at the School of Medicine, University of Pisa; and autoantibodies causing exophthalmos and goiter, with scientists at the University of Florence. This section also is working on the latter topic with a clinical endocrinologist in San Paulo, Brazil. Another investigator in the Laboratory of Biochemistry and Metabolism, who works on the molecular genetics of the genes involved in Tay-Sachs disease, has a continuing collaboration with a cell biologist at the Tel Hashomer Hospital, Tel Aviv, Israel, who also is studying Tay Sachs patients.

Laboratory of Molecular and Cellular Biology: A group of investigators in this Laboratory maintains an active collaboration on viral gene regulation studies with groups of scientists at Dunedin, New Zealand; Beersheba, Israel; and Bern, Switzerland. Another group continues an active collaboration on mammary gland biology with groups in Tokyo, Japan; Modena, Italy; and at the University of Shimane, Japan.

Laboratory of Cellular and Developmental Biology: The Laboratory of Cellular and Developmental Biology, in two collaborations with foreign scientists, continues its investigative efforts to determine the structure of the core particle, the fundamental unit of the chromosome, by using cloned DNA fragments

that interact precisely with histones. These studies, which began with definition of interactions at the NIH, continued with collaborative development of the genetically engineered DNA sequence and are in the phase of X-ray crystallographic analysis of the complex now being done by scientists at the Eidgenossische Technische Hochschule, Switzerland, and at the Medical Research Council, United Kingdom.

The Section on Medicinal Chemistry has been working with scientists in the Department of Medicine and Pathology, Sackler School of Medicine, Tel Aviv University, Israel, on producing varying structures of colchicine, a naturally occurring drug, and in using these compounds in biologic-screening assays for therapeutic properties in experimental amyloidogenesis. These studies suggest that 3-demethylthiocolchicine may be a potential replacement for colchicine.

Mathematical Research Branch: The Mathematical Research Branch (MRB) has a collaborative research effort involving reassessment of the quantitative application of cable theory, formulated for dendritic neuronal integration in light of recent higher-resolution anatomic and electrophysiologic data. This collaboration involves investigators in:

- The Department of Neurobiology, Hebrew University, Jerusalem, Israel;
- The Department of Physiology, University College, Oxford, United Kingdom;
- The John Curtin School of Medicine, Canberra, Australia; and
- The Laboratory of Neurochemistry, National Institute of Neurological and Communicative Disorders and Stroke, NIH.

This group of workers conferred in August 1987 at a 3-day workshop supported by the Neuroscience Institute, Rockefeller University.

NIH Visiting Fellows from Hungary and from Mexico worked on computational methodologies for analysis of molecular sequence data and upon the mathematic structure of models for bursting electrical activity of excitable cells. The Laboratory of Molecular Biology also has had Visiting Lecturers from Chile, Federal Republic of Germany, India, and Japan during the year.

Metabolic Diseases Branch: The Molecular Pathophysiology Section has three international collaborations involving GTP-binding proteins. Scientists in the Department of Pharmacology, Glasgow University, Scotland, use antibodies developed at the NIH to study mechanisms of signal transduction. Several publications came from this collaboration in 1987, of which the most significant showed that a key GTP-binding regulatory protein is deficient in the liver of a diabetic animal model. Another collaboration with a former Visiting Fellow who is now in the Pharmacology Institute, Heidelberg University, Federal Republic of Germany, has resulted in identification of a novel GTP-binding membrane protein that was purified from neutrophils and was found to be critical for their normal process of phagocytosis. A 2-year collaboration with investigators in the Department of Chemical Immunology, Weizmann Institute, Israel, has focused on possible connections between the tyrosine kinase class of growth factor receptors and the family of signal-transducing proteins. New insights into the mechanism of visual transduction were provided by studies showing that insulin-like growth factor receptors are present on rod photoreceptor cell membranes and that such receptors can phosphorylate the retinal protein, transducin.

Laboratory of Chemical Biology: The Laboratory of Chemical Biology is studying the intracellular polymerization of sickle hemoglobin with four cooperating foreign units:

- Department of Hematology, University of Birmingham Medical School, United Kingdom;
- Unit 48, Institut National de la Santé et de la Recherche Médicale (INSERM), Hôpital de Bicêtre, Paris, France;
- MRC Unit-Kingston, University of the West Indies, Kingston, Jamaica; and
- Department of Hematology, Sydney Hospital, New South Wales, Australia.

Work with Birmingham hematologists has involved analyses of the effects of varying amounts of polymer upon red blood cell filtration and has shown that very small amounts of polymer can decrease markedly the deformability of red blood cells. The studies with INSERM involve development of a more precise physicochemical model to account for the polymerization that occurs at very high oxygen-saturation levels. The NIH-Jamaican analyses of factors that account for the variability in severity of different individuals with the same sickle-cell syndrome are continuing. The hemoglobin polymerization in red cells that contain hemoglobin Setif is the focus for the collaboration with the Australian hematologist.

The Laboratory of Chemical Biology also is collaborating with the Kabigen Company, Stockholm,

Sweden, as part of the intramural research program on acquired immunodeficiency syndrome. The Laboratory has produced large quantities of the *tat* protein of human immunodeficiency virus for structural and genetic studies and has inserted the cloned gene for *tat* into an expression vector; Kabigen is producing the protein in *Eschechia coli*. After initial affinity chromatography in Sweden, the protein purification will be completed at NIDDK.

The Section on Protein Chemistry and Conformation and the Institute of Chemical Industry, University of Padova Faculty of Engineering, Italy, have been cooperating to solve two problems hampering total synthesis of cytochrome c. As part of this 10-year collaboration:

- Cytochrome c synthase has been found in yeast and beef heart mitochondria and solubilized;
- A method for joining two large fragments to form apocytochrome c has been developed in this section; and
- The two laboratories are working on total synthesis of cytochrome c as the underpinning for investigation of the roles of evolutionary invariant residues in the structure and function using, in addition to other methods, atomic substitution, addition, deletion, and labeling for residues being studied.

Eleven foreign scientists have worked in the Clinical Endocrinology Branch during FY 1987. Two are Fogarty Scholars from the National Institute of Medical Research, Mill Hill, London, England, and from Kyoto University, Japan. Visiting Scientists, Associates, and Scholars come from Italy (4): Universities of Rome, Catania, and Naples (2); University of Porto Allegra, Brazil; Ajinomoto Company, Japan; University of Ioannina, Greece; Indian Institute of Technology, New Delhi, India; and University of Tokyo, Japan. Studies of thyroid hormone metabolism have compared intracellular transport of the active hormone, L-T3, and its inactive enantiomer, D-T3, and shown the responsible mechanism to be outside of the nucleus and probably at the plasma membrane; have shown that availability of T3 within nerve cells may be regulated at the plasma membrane by variation in the uptake of T4; and investigated changes in L-T3 cell and nuclear uptake in neuroblastoma cells differentiated by exposure to sodium butyrate. Studies of thyroid hormone action determined the heterogeneity of the 3"-untranslated region by S1 nuclease mapping and that rats given triiodothyronine had an increased proportion of chromatin displaying malic acid gene hypersensitivity.

The Laboratory of Chemical Physics (LCP) has had Visiting Fellows working on the following studies:

- A Fellow from Israel worked on the use of a fungus, *Beauvaria sulfurescens*, to hydroxylate unactivated methylene groups and on synthesis of a hapten for studies of the use of antibodies to imitate enzymatically catalyzed reactions;
- A Fellow from Japan conducted research on red blood cells and their ghost deformability in flow, especially on ghost changes caused by ATP, Ca++, chlorpromazine, and other compounds;
- A Fellow from China separated diastereomeric esters of several aromatic benzyl alcohols;
- A Fellow from the United Kingdom applied vibrational infrared and Raman spectroscopic techniques to intact and model membrane assemblies whose bilayer lipids form novel, interdigitated lipid chain phases;
- A Fellow from France developed and applied improved magnetic resonance imaging methods for study of the structure and conformation of biologically active molecules; and
- A Fellow from Iran set up an experimental system to measure multiphoton resonance fluorescence and pT phosphorescence that is being tested on benzene.

Chapter XII
National Institute of Environmental Health Sciences

Introduction

The National Institute of Environmental Health Sciences (NIEHS) is the principal Federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health. As such, it is concerned with not just a single disease state or a single organ but the whole spectrum of diseases and organs as they are induced or affected by environmental factors. Resulting adverse effects can be subtle, chronically debilitating, or acute. These include, but are not limited to, neurologic and behavioral disorders, respiratory disease, cardiovascular disease, biochemical and endocrine disturbances, kidney dysfunction, carcinogenesis, mutagenesis, reproductive disorders, birth defects, developmental disabilities, and subtle effects such as immune suppression. NIEHS concentrates research into all possible outcomes of the widest possible range of environmental exposures.

In its research, NIEHS seeks to identify and characterize potentially harmful environmental agents, particularly toxic chemicals. These studies include a variety of biologic systems and test the results of carefully controlled exposures to hazardous agents. Which disease processes are initiated or aggravated by environmental agents and the extent of exposure of various population groups, especially sensitive populations, to these agents are documented. NIEHS supports efforts to identify hazardous agents before they are released into the environment. These include developing, testing, and validating biologic assay systems to ascertain animal toxicity and thus to predict toxic effects that might occur in humans. Such efforts transcend national boundaries, and NIEHS plays a leading role in the organization and development of international research into environmental health and chemical safety problems.

Highlights of Recent Scientific Advances Resulting From International Activities

In order to prevent or minimize the adverse effects of environmental factors, adequate methodologies must be developed to predict the toxicity of these factors. NIEHS scientists, in collaboration with scientists throughout the world, through multilateral and bilateral agreements, have played a leading role in evaluating current methods and developing better methodologies for assessing the toxic potential of environmental chemicals. Major emphasis has been on international collaboration aimed at developing better, short-term methods for detecting whether chemicals can cause such toxic effects as genetic mutations, birth defects, and damage to various organ systems. Most current methods are expensive, time-consuming, and often not adequately sensitive, but the large number of chemicals in production and entering the marketplace makes imperative more efficient and accurate test methods. A number of test systems are being reviewed, evaluated, and validated in laboratories throughout the world through the International Program on Chemical Safety. This program also provides for a multilateral mechanism to coordinate the exchange of information on the toxicologic testing of chemicals. Such information exchange is essential, because many countries lack the resources to conduct extensive testing programs. A coordinated information exchange program on the testing of chemicals will help prevent unnecessary duplication of resource use.

In recent years, considerable progress in understanding how genes work has allowed scientists to identify environmental hazards, predict which people are most susceptible to them, and develop ways to prevent environmentally induced illnesses. Continuing in-

ternational collaborative research on cloning and molecular characterization of genes will aid in defining how chemicals interact with DNA and will help identify sentinel reactions by which damage to DNA in human cells can be detected. Detection of damage to DNA has important implications for carcinogenesis and heritable genetic diseases. It has been shown that a number of factors interact to determine the ultimate action of chemical mutagens and carcinogens. Under the U.S.-Japan Cooperative Medical Sciences Program, scientists from both countries have identified dietary factors capable of enhancing or inhibiting the mutagenic activity of substances found in food. They have isolated and identified mutagenic and carcinogenic compounds from broiled fish and ground beef. Additional tests are being conducted with a variety of other foods that can reduce the activity of the mutagens in cooked meats. These studies promise to provide knowledge that may make it possible to prevent cancer and genetic diseases in which diet is a contributing factor.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

NIEHS conducts scientific exchanges and collaborative research through a variety of mechanisms that extend from informal direct contact between investigators in a number of countries to formal agreements for cooperation between the United States and the governments of other countries.

China: Cooperation between the United States and China in the area of environmental health was initiated during 1980 under the U.S.-China Agreement for Cooperation in the Science and Technology of Medicine and Public Health. NIEHS is a participant in public health and health services research, which includes environmental and occupational health concerns. Since then, discussions in the following areas have been held during exchange visits:

- Reproductive and developmental toxicology;
- Validation of short-term test methods to detect and assess carcinogens, mutagens, and teratogens in the environment; and
- Extrapolation of laboratory animal data to humans.

NIEHS scientists have given research seminars at institutions in China and have hosted the visits of numerous Chinese scientists to discuss research programs of mutual interest. During 1987, the Director, NIEHS, was the DHHS delegate to the U.S.-China Joint Commission on Science and Technology Meeting held in Beijing. The status and progress of various collaborative areas were reviewed and potential new areas of cooperation were identified.

Egypt: Cooperation between American and Egyptian health scientists has been carried out under the auspices of the U.S.-Egypt Joint Working Group on Health Cooperation (JWGHC). NIEHS is assigned responsibility for the U.S. Subcommittee on Environmental and Occupational Health of the JWGHC. Efforts to date have consisted of workshops held in Egypt on the biomedical impacts of technology transfer, pesticides, trace metals, radiation, environmental management, and mutagenesis. Efforts to establish an Information Unit for Environmental Impact Assessment are also continuing. This Information Unit, located at the Environmental Health Center in Cairo, provides the Egyptian Ministry of Health and Egyptian institutions and universities access to information on environmental and occupational health hazards, thus strengthening the scientific base for research and regulatory decisionmaking.

Finland: A Memorandum of Understanding on Collaboration between NIEHS and the Finnish Institute of Occupational Health, Helsinki, was made formal in FY 1983. Since then, a number of exchange visits have taken place between U.S. and Finnish scientists to share information on:

- Pharmacokinetics;
- Reproductive toxicology;
- Genetic toxicology;
- Epidemiology;
- Risk assessment; and
- Strategies for setting priorities for toxicologic research.

NIEHS and the Finnish Institute of Occupational Health also co-sponsored an international workshop on occupational hazards caused by polychlorinated biphenyls and chlorobenzenes in capacitors and transformers.

India: NIEHS and National Toxicology Program (NTP) scientists have been cooperating with India by conducting experimental animal studies on the toxicity of methyl isocyanate, the chemical responsible for the industrial disaster in Bhopal, India, in December 1984. During FY 1987, several NIEHS scientists visited research and government organiza-

tions in India to discuss NTP's research findings on the toxicity of methyl isocyanate. NIEHS also sponsored and hosted an international conference entitled the "Toxicity of Methyl Isocyanate" and hosted the visits of a number of scientists from India to discuss toxicologic research activities.

Italy: Cooperation between American and Italian health scientists has taken place since 1977 under a Memorandum of Understanding between the U.S. Department of Health and Human Services and the Italian Ministry of Health. Since then, a number of exchange visits have taken place to share information on the bioavailability of 2,3,7,8-tetrachlorodibenzodioxin, studies on the chemical contamination of drinking water, chemical selection procedures, and the design and interpretation of 2-year toxicity studies. During FY 1987, the Director, NIEHS, also met with the Italian Minister of the Environment to discuss potential future collaborative research activities.

Japan: Cooperation between American and Japanese scientists on environmental health problems takes place under two formal agreements: The U.S.-Japan Cooperative Medical Sciences Program and the Agreement on U.S.-Japan Cooperation in Research and Development in Science and Technology. Under the U.S.-Japan Cooperative Medical Sciences Program, American environmental health scientists participate in the Panel on Environmental Mutagenesis and Carcinogenesis. The Director, Division of Biometry and Risk Assessment, NIEHS, and the Assistant to the Director for International Programs, NIEHS, serve as panel members. Joint areas of research focus on the detection of mutagenic and carcinogenic chemicals, using both *in vitro* and *in vivo* test systems, and on monitoring human populations for evidence of exposure to mutagenic and carcinogenic chemicals. The Director, NIEHS, serves as a State Department-appointed member of the Joint Committee, which oversees the overall activities of the U.S.-Japan Cooperative Medical Sciences Program. During FY 1987, the Director, NIEHS, the Associate Director for Genetics, NIEHS, and the Assistant to the Director for International Programs participated in the 15th U.S.-Japan Joint Environmental Panel Conference entitled "Approaches for Human Population Monitoring," held at Lawrence Livermore National Laboratory, Livermore, California. Also during FY 1987, the Director, NIEHS, participated in the U.S.-Japan Joint Subcommittee Meeting on Program Review and Planning and the 23rd U.S.-Japan Joint Committee Meeting.

Under the U.S.-Japan Agreement on Cooperation in Research and Development in Science and Technology, NIEHS participates in the toxicology program area in the counterpart working group on health. Cooperative activities under this agreement focus on good laboratory practices, test method development, and the testing of chemicals for mutagenic, carcinogenic, and other toxic effects. Formal mechanisms for the mutual exchange of information on the testing of chemicals have been established under this agreement. In FY 1987, annual exchange visits between Japanese and NIEHS scientists continued, and both sides have shared information on test method development, which chemicals will be tested, and test results. Several test systems are being reviewed and validated in both U.S. and Japanese laboratories, and collaborative activities on oncogenes are continuing.

In addition to these activities, the Director, Biometry and Risk Assessment Program, NIEHS, continues his collaboration with the Radiation Effects Research Foundation, Hiroshima, to analyze the long-term health effects on victims of the atomic bomb.

U.S.S.R.: Cooperation between U.S. and Soviet environmental health scientists takes place under two formal agreements: the U.S.-U.S.S.R. Medical Science and Public Health Cooperative Agreement and the U.S.-U.S.S.R. Agreement on Cooperation in the Field of Environmental Protection. Under the Medical Science and Public Health Cooperative Agreement, scientists from both countries are conducting joint research on the biologic effects of low-frequency electromagnetic radiation; 1987 marked the 15th year of formal collaboration in environmental health research between the United States and the Soviet Union. A large amount of scientific information has been exchanged during these years. Cooperative research efforts have involved formal workshops, collaborative research projects, and exchange visits between scientists of both countries. Duplicate collaborative experiments to evaluate sensitive tests for determining the biologic effects of electromagnetic fields on the nervous system and to validate research results obtained in the United States and the Soviet Union have been completed.

NIEHS also participates in the U.S.-U.S.S.R. Agreement on Cooperation in the Field of Environmental Protection, which is administered for the United States by the Environmental Protection Agency. The Director, NIEHS, serves as DHHS representative to the Environmental Protection Agreement and co-chairman of the working group concerned with the biologic and genetic effects of pollution. Exchange visits under this agreement have been conducted in research areas concerned with the mutagenic effects of environmental contaminants.

Yugoslavia: Under the auspices of the U.S.-Yugoslavia Joint Board for Scientific and Technological Cooperation, NIEHS scientists continued collaborative studies on the influence of DNA repair in bacteria on the low-dose mutagenicity of alkylating agents.

Taiwan: Collaborative studies between U.S. and Taiwanese scientists are carried out through a Cooperative Program in the Biomedical Sciences between the American Institute in Taiwan and the Coordination Council for North American Affairs. For the past 5 years, NIEHS scientists from the Biometry and Risk Assessment Program have collaborated with Taiwanese scientists in studies investigating the effects of accidental human exposure to polychlorinated biphenyls (PCBs) in Taiwan. Studies on the effects of PCB exposure on enzymatic activity in human tissues suggest a potential for substantial and persistent effects of these pollutants on human metabolism. NIEHS and Taiwanese scientists are conducting a collaborative clinical survey of a cohort of children exposed transplacentally to PCBs and related chemicals. Preliminary data show that the children have abnormalities of pigment, nails, teeth, and skin and show a developmental delay on a number of dimensions.

Activities With International and Multinational Organizations

World Health Organization: NIEHS staff have been active participants in World Health Organization (WHO) programs for a number of years, and WHO designated NIEHS a Collaborating Center for Environmental Health Effects in 1975. As a Collaborating Center, NIEHS provides advice and scientific expertise to WHO Headquarters and WHO Regional Offices and assists them in the formulation of research programs related to the biomedical aspects of environmental pollution.

International Agency for Research on Cancer: NIEHS also collaborates with the WHO International Agency for Research on Cancer (IARC). Collaborative efforts include the establishment of a registry of cohorts of individual workers exposed to phenoxy acid herbicides and their contaminants. Although exposure to phenoxy acids and chlorophenols has been and continues to be widely spread throughout the environment, published epidemiologic studies on such exposures have not resolved the question of the potential cancer risk to humans posed by such exposures. Analysis of the registry's data could provide insight into this public health issue. During FY 1987, scientists from NIEHS participated in a number of IARC-sponsored expert working groups to prepare "IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans." These monographs collect all available relevant experimental and epidemiologic data about a chemical or groups of chemicals to which humans are known to be exposed and summarize the evidence for the carcinogenicity of chemicals and other relevant information.

International Program on Chemical Safety: In 1979, WHO established the International Program on Chemical Safety (IPCS), a cooperative undertaking involving WHO, the United Nations Environment Program, the International Labor Organization, and their member states.

The major objectives of the IPCS are:

- To encourage international cooperation in health and environmental risk evaluations of priority chemicals (including dissemination of information);
- To develop methodology for health and environmental risk assessments;
- To develop response mechanisms for coping with chemical emergencies that may be international in scope; and
- To promote training and development of manpower in the field of chemical safety.

The IPCS provides an effective multilateral mechanism for dealing with global environmental health issues and avoiding costly duplication of national efforts to test and assess chemicals.

In October 1980, a cooperative agreement was signed between NIEHS and WHO, and NIEHS assumed the function of a participating institution within the IPCS for such activities as international evaluation of the biologic effects of chemicals and health hazard assessments and review and validation of methods for testing of mutagenicity, carcinogenicity, neurobehavioral toxicity, and toxicity to reproductive function. In September 1986, the Agreement was extended for another 3 years. A WHO Interregional Research Unit, housed at NIEHS, was established in 1981 to assist the Central Unit established at WHO Headquarters in coordinating the activities of the IPCS participating institutions. During 1987, NIEHS hosted an informal meeting of representatives of IPCS participating institutions from the American Region. The Director, Environmental Health, WHO, and the Manager, IPCS, reviewed the IPCS activities and the participating institutions discussed their work as it relates to the objectives of IPCS. The meeting greatly facilitated an exchange of information and

may lead to joint activities between participating institutions under the IPCS umbrella.

Since the inception of the IPCS, numerous scientific experts from NIEHS have participated on IPCS committees, special consultations, conferences, and technical working groups. The Director, NIEHS, serves as a member of the IPCS Program Advisory Committee and chaired it during the program's first 2 years of operation. This committee, composed of members designated by the Director-General of WHO, is the general oversight body providing advice on the policies and priorities of the IPCS. The Fifth Program Advisory Committee meeting was held in Geneva in FY 1987. The Director, NIEHS, attended this meeting and the Assistant to the Director for International Programs served as rapporteur.

A number of NIEHS scientists continued to play a leading role in the IPCS "Collaborative Study on Short-Term Tests for Genotoxicity and Carcinogenicity." Also during 1987, NIEHS staff continued to review IPCS criteria documents, working papers, and proposed projects.

During FY 1987, NIEHS staff participated in the international meeting of the Scientific Group on Methodologies for the Safety Evaluation of Chemicals (SGOMSEC), dealing with methods to reduce injury resulting from chemical accidents. SGOMSEC is an IPCS activity sponsored jointly with the Scientific Committee on Problems of the Environment of the International Council of Scientific Unions. The Director and the Assistant to the Director, NIEHS, participated in a SGOMSEC planning meeting in 1987 to outline the workshop on "Methods to Assess the Adverse Effects of Pesticides on Non-Vector Targets," to be held in Czechoslovakia in 1988.

In other WHO activities, a scientist from the Laboratory of Reproductive and Developmental Toxicology, NIEHS, continued to serve as a member of the Toxicology Review Panel of the WHO Special Program of Research in Human Reproduction. The review panel meets twice a year to consider the potential toxicity associated with current and future approaches to contraception.

Extramural Programs

Through its extramural programs, NIEHS provided grant support to:

- The Karolinska Institute, Sweden, to study the effects of environmental agents on the endocrine system;
- York University, Canada, to study the development of a yeast system to detect potential genetic defects caused by chemicals;
- Princess Alexandria Hospital, Queensland, Australia, to evaluate new approaches to paraquat intoxication therapy;
- The State University of Leiden, Netherlands, on mechanisms of genotoxicity; and
- The World Health Organization, for support of the International Program on Chemical Safety.

NIEHS also supported contracts to:

- The Institut für Mikrobiologie Technische Hochschule, Federal Republic of Germany, to validate a yeast aneuploidy test system and use it for the testing of chemicals that might cause mitotic and meiotic aneuploidy; and
- The Inveresk Research Institute, Scotland, to compare the mutagenic response of various chemicals in the mouse lymphoma assay and the Chinese hamster ovary assay.

International Conferences, Seminars, and Meetings

To provide an opportunity for scientists from different countries to exchange research results and stimulate scientific collaboration, NIEHS continues to organize, fund, and participate in international scientific conferences and seminars. NIEHS organized and supported international meetings and conferences in the following areas during FY 1987:

- Fifth International Neurotoxicology Conference, "Cognitive Dysfunction in Children and Adults";
- Comparative Ovarian Pathology Conference;
- Role of Biomarkers in Reproductive and Developmental Toxicology;
- International Conference on Tumor Promotion;
- Health Effects of Nitrogen Oxides; and
- Third Conference on Estrogens in the Environment, "Influences on Development."

Papers from each of these meetings will be compiled for publication in scientific journals including the NIEHS journal, *Environmental Health Perspectives*, or as full-length books, to serve as definitive references for future research in these areas.

During FY 1987, NIEHS scientists also accepted invitations to chair sessions and present scientific papers at a number of international meetings, which included the following:

- Symposium on Mineral Fibers in the Non-Occupational Environment, Lyon, France;
- 10th International Congress of Pharmacology, Sydney, Australia;

- Second World Congress of Neuroscience, Pecs, Hungary;
- European Congress of Endocrinology, Copenhagen, Denmark;
- International Conference on Structure-Activity Relationship for Toxicological Estimation of Chemicals, Pisa, Italy; and
- European Environmental Mutagen Society meeting, Zurich, Switzerland.

Intramural Programs and Activities

NIEHS scientists from various intramural laboratories are involved in a broad range of collaborative activities with scientists from a number of different countries which produce information important to the Institute's research goals.

The Laboratory of Reproductive and Development Toxicology is involved in cooperative studies with the University of Calgary, Canada, on the origin and migration of primordial germ cells, and with the University of Geneva, Switzerland, on the distribution of neural peptides in the human brain. In addition, collaborative activities are continuing with the University of Wurzburg, Federal Republic of Germany, on the metabolism of estrogenic xenobiotics. This research has recently established new intracellular targets for estrogen carcinogenicity.

The Laboratory of Molecular Biophysics continues to collaborate with scientists from the University of Buenos Aires, Argentina, on the mode, action, and toxicity of antiparasitic compounds used in the treatment and prevention of South American trypanosomiasis (Chagas' disease), and in the treatment of anaerobic protozoal infections such as trichomoniasis, amebiasis, and giardiasis.

The Laboratory of Pulmonary Pathobiology is conducting collaborative research with colleagues from France on the secretion of prostaglandins by pulmonary macrophages.

The Toxicology and Research Testing Division continues to collaborate with scientists from a number of countries on the validation of short-term test methods for detecting genotoxicity.

As part of the Institute's participation in the NIH Visiting Program, the NIEHS intramural program was host to 63 Visiting Fellows, Associates, Scientists, and Guest Researchers from 17 countries during FY 1987. They came from Australia, Brazil, Canada, China, Colombia, Federal Republic of Germany, Finland, India, Iran, Italy, Japan, Lebanon, Netherlands, Poland, South Korea, Sweden, Switzerland, United Kingdom, and Taiwan. Examples of collaborative research projects conducted by these scientists include studies on:

- The role of tumor suppressor genes in carcinogenesis;
- The inhibition of *in vitro* transformation by retinoids;
- The effects of pulmonary proteins and lipids on the interactions between toxic particles and alveolar macrophages;
- The identification of stage-specific proteins synthesized by isolated spermatogenic cells;
- The development of new analytical techniques for the detection of catechol estrogens;
- The characterization of subpopulations of Leydig cells in the interstitium of the testis;
- The development of new test methods for neurobehavioral toxicity;
- The role of oncogenes in carcinogenesis;
- Mechanisms of nephrotoxicity and reproductive toxicity caused by environmental agents;
- Molecular biology of cytochrome P-450;
- The mechanisms of the organic anion transport system and its role in regulating the rate of elimination of foreign compounds;
- Rodent tumor classification;
- Statistical design and data analysis for carcinogenicity studies;
- The role of essential trace metals and metallothionein in the pathogenesis of cadmium-induced nephropathy; and
- Mutational mechanisms in eukaryotes, using yeast as a model.

These research projects were of mutual benefit to U.S. and foreign scientific endeavors and produced valuable scientific information important to the Institute's research goals. Also during FY 1987, administrators and scientists from all parts of the world visited NIEHS to be briefed on its programs and activities.

Chapter XIII
National Institute of General Medical Sciences

Introduction

The National Institute of General Medical Sciences (NIGMS) was established by Congress in the fall of 1962 as an expansion of a Division organized in 1958 by the Secretary of the Department of Health, Education, and Welfare. The mission of NIGMS is to support basic research and research training in biomedical, natural, and behavioral sciences. Applications for project grants in basic research from investigators in foreign institutions are accepted and processed by the National Institutes of Health and NIGMS. Research projects in foreign countries are supported by NIGMS exclusively within its extramural activities.

The Institute's activities are organized and conducted through five operating programs: Cellular and Molecular Basis of Diseases; Genetics; Pharmacological Sciences; Biophysics and Physiological Sciences; and the Minority Access to Research Careers (MARC). Each program fosters multidisciplinary approaches and, except for the MARC Program, employs the full range of support mechanisms: research project grants, program project grants, research center grants, and institutional and individual fellowships. Research in foreign countries is supported exclusively by research project grants.

Cellular and Molecular Basis of Disease Program

The Cellular and Molecular Basis of Disease Program seeks a greater understanding of the structure and function of human cells with the ultimate goal of finding ways to prevent, treat, and cure diseases that result from disturbed or abnormal cellular and molecular activity. Investigations receiving support are broadly concerned with the biochemical description and analysis of molecular events in normal and diseased cells and with the structure and function of organelles and membranes at the molecular and subcellular levels. Areas of research emphasis include:

- Development of knowledge of subcellular organelles and their constituents to elucidate more precise concepts of how the cell functions as a unit;
- Cell-cell interactions during morphogenesis;
- Mechanisms of enzyme catalysis and regulations; and
- Elucidation of the relationship between chemical structure and biologic activity.

Genetics Program

The Genetics Program is directed toward gaining a better understanding of fundamental genetic processes and the mechanisms of inheritance in health and disease. Its objectives are to support research on the prevention, therapy, or cure of human genetic diseases and thus complement the more targeted efforts of the disease-oriented Institutes of NIH. The program focuses on such basic topics as the mechanisms of transmission and expression of genetic information, genetic controls, and the dynamics of genes in populations of organisms. Prokaryotic and eukaryotic organisms are extensively employed in this type of research.

Pharmacological Sciences Program

The Pharmacological Sciences Program supports a broad spectrum of research. Its aim is to provide an improved understanding of the biologic phenomena and related chemical and molecular processes involved in the actions of therapeutic drugs, anesthetics, and biologically active chemicals and their metabolites.

The program takes a multifaceted approach to pharmacologic problems that have implications for several disease areas. Its goals are to:

- Study the molecular mechanisms of chemical and biologic interactions of drugs with receptors;

- Investigate the interaction of drugs with endogenous mediators of physiologic responses;
- Determine metabolic pathways and mechanisms of drug actions in human and other biologic systems;
- Elucidate the structure of active drug metabolites and intermediates;
- Study mechanisms of adverse drug reactions and toxicity of therapeutic drugs;
- Support new approaches to the synthesis of compounds of biologic interest;
- Promote the design of new and controllable methods of drug delivery;
- Investigate the pharmacology of therapeutic drugs in children;
- Elucidate the ways in which anesthetic agents modulate pain; and
- Discover genetic and environmental variables that influence drug action.

Biophysics and Physiological Sciences Program

The major objectives of the Biophysics and Physiological Sciences Program are to foster:

- The application of physical and engineering principles to the study of the physical and molecular structures of biologically important substances;
- The development and improvement of instruments, devices, and methodologies for the advancement of biomedical sciences; and
- The broadening and strengthening of the scientific base in those areas of clinical and physiologic sciences related to all aspects of treatment, recovery, and rehabilitation of trauma and burn injury.

Summary of International Programs and Activities

Activities With International and Multinational Organizations

GenBank®: GenBank® is a contract awarded to Intelligenetics, Inc., for the maintenance and distribution of a data base consisting of all published DNA sequences. The contract is funded by NIGMS with additional funding from the National Science Foundation; Department of Energy; Department of Agriculture; National Cancer Institute; Division of Research Resources; National Heart, Lung, and Blood Institute; and National Library of Medicine.

The sequences data are entered under subcontract to Los Alamos National Laboratory. Distribution is via magnetic tape, floppy diskettes, a printed compendium, and an on-line service. The success of GenBank® depends on active collaboration with the European Molecular Biology Laboratory at Heidelberg, Federal Republic of Germany, which maintains a similar data base. Each of these groups enters about half of the published data and then shares the data to prepare the complete data base. Recently, collaboration has been extended to a Japanese effort headed by Dr. Takeo Maruyama, of the National Institute of Genetics. As part of this effort, data appearing in Japanese journals will be entered and shared with GenBank® and the European Molecular Biology Laboratory.

Extramural Programs

Principal investigators in appropriate research establishments in foreign countries are eligible to submit research project grant requests to NIH. Those foreign applicants who are appropriate for assignment to NIGMS compete for funding on the same basis as all other applicants. NIGMS funded 23 grants to principal investigators in Canada, Chile, Israel, Spain, and Switzerland during FY 1987.

International Conferences, Seminars, and Meetings

NIGMS joined other NIH Institutes to provide foreign travel for American and foreign scientists to participate in the:

- International Conference on Quantitative Genetics;
- International Symposium on Plant Transposable Elements;
- Ninth International Biophysics Congress;
- Ninth International Flavins and Flavoproteins Symposium;
- Ninth International Workshop on Human Gene Mapping; and
- 10th International Union of Pharmacology Conference.

Chapter XIV
National Institute of Neurological and Communicative Disorders and Stroke

Introduction

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is the NIH unit responsible for research on the causes, treatments, and prevention of nervous system diseases and disorders of speech, language, and hearing. To pursue every avenue of research that promises to reveal new information about the brain and ways to overcome disorders of the nervous system and senses of communication, the Institute supports scientists in medical institutions around the globe. International support takes various forms:

- Joint research conducted under country-to-country agreements;
- Efforts involving multinational organizations;
- Research grants and training programs;
- Collaborative research projects uniting NINCDS scientists and their foreign colleagues;
- A Special Foreign Currency Program (P.L. 480) that allows use of U.S.-owned foreign currencies overseas; and
- International meetings to share knowledge.

Neurological disorders touch lives everywhere in the world, maiming and killing old and young, rich and poor. An infant born in a Mexican village cannot sit upright because hydrocephalus has swollen his head with fluid; a young adult in the Seychelles lies in bed slowly dying, her legs paralyzed by tropical spastic paraparesis; an elderly American no longer recognizes his face in the mirror because of Alzheimer's disease. Scientists fighting such neurological disorders confront not one adversary but a host of enemies that includes flawed genes, viruses, cancers, blood clots, nutritional deficiencies, and traumatic injuries.

The vast geographic range of nervous system diseases and their varied origins make international scientific collaboration imperative. Often the very diversity of these disorders supplies the clues needed to discover weapons against them. Thus, scientists concentrating on epilepsy search for reasons why Africans and South Americans are more frequently afflicted with the disorder than Americans. Similarly, investigators trying to understand the etiology of multiple sclerosis are gaining surprising insights from colleagues working with myelopathy.

Highlights of Recent Scientific Advances Resulting From International Activities

This year, NINCDS undertook a major new international initiative against one of the world's top killers—stroke. Through a grant awarded to a Canadian medical center, the Institute has begun a collaborative clinical trial to determine whether a commonly performed operation to prevent stroke actually works.

The operation, carotid endarterectomy, clears fatty deposits from arteries that supply blood to the brain. In the United States alone, surgeons perform more than 130,000 carotid endarterectomies annually.

The newly funded study, led by scientists at the John P. Robarts Research Institute in London, Ontario, will focus on symptomatic stroke patients who have had a transient ischemic attack, a brief interruption of blood flow to the brain that quickly resolves itself. The study will weigh the benefits and risks of carotid endarterectomy and produce a guideline that will enable physicians to decide which patients are most likely to benefit from the procedure.

Patients participating in the study will all receive top-quality medical care, including antihypertensive treatment as necessary, and counseling about smoking and diet. Additionally, half of the study group will undergo a carotid endarterectomy. All patients will be monitored for 5 years.

Results from the Canadian study will be compared with those from another NINCDS-supported investigation under way in the United States to assess whether carotid endarterectomy reduces stroke in asymptomatic patients (those who have a partially blocked carotid artery but have not suffered a transient ischemic attack).

NINCDS also is continuing its longstanding efforts against Huntington's disease (HD), an inherited disorder of midlife onset in which premature brain-cell death causes progressive loss of mental and motor skills. This year, collaboration by U.S. and Venezuelan scientists led to several important advances:

- Discovery of a second marker gene, knowledge of whose location should speed the mapping and cloning of the HD gene itself;
- Verification of the first marker gene's persistent inheritance along with the HD gene in all families tested; and
- Finding of a new Venezuelan HD pedigree with at least 255 members.

HD pedigrees from Venezuela are proving invaluable for investigations of other diseases. The pedigrees form a genetic data bank that has enabled scientists to identify marker genes on chromosome 21 for both Alzheimer's disease and Down syndrome.

Still more knowledge about Alzheimer's and Down syndrome resulted from a collaborative effort uniting NINCDS intramural investigators with French scientists working at the Laboratoire de Biochimie Génétique in Paris, France. The scientists found that patients with nonfamilial Alzheimer's disease and some types of Down syndrome have an extra copy of the gene involved in making amyloid, a substance found in high concentrations in the brains of Alzheimer's patients. The patients studied had three rather than the normal two copies of the amyloid gene. Moreover, patients with both disorders had the abnormal gene duplication on the same critical segment of chromosome 21, helping to explain why those with Down syndrome often develop Alzheimer's if they live long enough.

Hearing loss, too, ranks high among disorders with global impact. NINCDS-supported scientists in Australia are closing in on an implantable device that would allow the profoundly deaf to hear. The device, a multiple-channel cochlear prosthesis, uses a tiny electronic stimulator and receiver to create hearing sensations. This year, the scientists, at the University of Melbourne in Victoria, implanted the device in deaf patients and are testing to see what types of hearing sensations occur.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

Two NINCDS country-to-country agreements focus on the formidable worldwide problem of controlling pain, and a third is directed toward discovering how to restore function to those who have suffered severe nerve damage.

China: The U.S.-China Bilateral Agreement marshals the expertise of NINCDS intramural scientists and their colleagues at the Shanghai Brain Research Institute, part of the Chinese Academy of Sciences, to explore how nerves communicate the sensation of pain. Other studies made possible by this agreement include epidemiologic surveys of stroke. People living in some areas of China face the world's highest risk of stroke.

Hungary: Under the U.S.-Hungary Bilateral Agreement, an NINCDS grantee at the University of North Carolina at Chapel Hill and collaborating Hungarian scientists are using immunocytochemical and recombinant DNA techniques to peer into the body's pain pathways and see how neurons there transmit messages with chemical agents.

Mexico: Under the U.S.-Mexico Bilateral Agreement, investigators from the NINCDS Laboratory of Neural Control and the National Polytechnic Institute's Center for Research and Advanced Studies in Mexico City are examining the role of spinal cord neurons in exciting motor neurons, nerve cells that help control muscle movement. Their findings may suggest ways to strengthen surviving motor functions in patients with damaged spinal cords.

Activities With International and Multinational Organizations

Since 1975, NINCDS has been one of 12 World Health Organization (WHO) Collaborating Centers in the Neurosciences. These centers, strategically positioned around the world, investigate neurological disorders and develop community prevention and treatment programs. Among the disorders studied are stroke, epilepsy, and neurological and communicative disorders related to childhood nutritional and developmental problems. The other 11 WHO Collaborating Centers in the Neurosciences are in the following countries: Canada, China (2), Colombia, France (2), Mexico, Nigeria, Senegal, Switzerland, and U.S.S.R.

Each WHO Center functions independently, supplying technical assistance and collaborative research and training. Centers also exchange scientific information by sponsoring conferences and courses and publishing proceedings of those events.

The NINCDS Neuroepidemiology Branch and WHO have collaborated on the creation of an international disease classification protocol that establishes uniform definitions for neurologic disorders. The protocol should help resolve problems in comparing data from different countries, and is now being used to estimate the prevalence of major neurological disorders in many parts of the world.

NINCDS and WHO, along with the NIH Fogarty International Center, also cooperate in a program aimed at multiplying the number of neuroscientists who are qualified and willing to undertake sophisticated investigations in more isolated, less developed regions. The International Neurosciences Fellowship Program brings investigators from developing countries to the United States for advanced research training. They subsequently return home to become leaders in neuroscience research and education in their own countries. During FY 1987, NINCDS welcomed six neuroscience Fellows from the following countries: China, India, Japan, Nigeria, Thailand, and Tunisia.

Extramural Programs

During FY 1987, NINCDS awarded 26 foreign research grants to the following countries: Australia (1); Canada (8); Ireland (1); Israel (7); Italy (1); Mexico (1); New Zealand (1); Portugal (1); Sweden (3); Switzerland (1); and United Kingdom (1).

A drug able to shrink some brain tumors is emerging from one NINCDS-supported Canadian investigation. Scientists at the Montreal Neurological Institute and Hospital in Quebec significantly reduced the size of malignant glial tumors with a drug known as BCNU. The investigators believe that the drug's effect derives partly from its greater absorption by tumor cells than by normal brain cells—a phenomenon verified with positron emission tomography scans. The investigators now are searching for other promising antitumor drugs and already have begun testing the potency of SarCNU and AspCNU.

Elsewhere, scientists are trying to find ways of restoring at least some mental and motor abilities to brain-damaged patients. At the University of Lund in Sweden, NINCDS-supported scientists are examining whether intracerebral grafts of certain neurons can enable brain-damaged rats to recover some behavioral and functional capabilities. Preliminary findings suggest that implanted nerve cells secreting the neurotransmitter norepinephrine can inhibit epileptic-type seizures. The scientists want to see how the implanted and host cells interconnect and how other neurotransmitters affect the action of grafted nerves. These studies should yield insights about such degenerative nervous system disorders as Parkinson's, Huntington's, and Alzheimer's diseases.

Through NINCDS-supported neuroepidemiologic studies in Ireland, a grantee at the Health Research Board in Dublin is testing the currently held theory that predicts escalating rates of multiple sclerosis as climates grow colder. The grantee is charting the prevalence of multiple sclerosis in two areas of Cyprus—a subtropical coastal zone and a frigid mountain province.

NINCDS also supports U.S. scientists who test promising anticonvulsant drugs developed by investigators in Europe. Through this program, administered by the NINCDS Epilepsy Branch, two drugs are currently undergoing clinical trials.

The NINCDS Epilepsy Branch works closely with the International League Against Epilepsy to formulate drug-testing standards, classify different types of epileptic seizures, and educate clinicians about effective administration of antiepileptic drugs. The League this year recognized the Institute's leading role in epilepsy research with two honors: The Chief of the Preclinical Pharmacology Section, NINCDS Epilepsy Branch, received the group's ambassador award for his work on antiepileptic drugs, and the Branch Chief became editor of the League's journal.

International Conferences, Seminars, and Meetings

Institute scientists undertook various initiatives in FY 1987 to forge new ties with their international colleagues. To help encourage new collaborative ventures, the NINCDS Director this year participated in the first-ever joint meeting of the International and American Societies for Neurochemistry (ISN/ASN). The meeting, convened in Caracas, Venezuela, drew attendees from Europe and Asia as well as North and South America. The NINCDS Director assumed the role of honorary chairperson for a special ISN/ASN satellite conference in Miami that focused on cellular and molecular aspects of neurodevelopment and regeneration.

In addition, the Institute Director chairs a WHO Task Force on Stroke and Other Cerebrovascular Diseases. At meetings this year in London and Geneva, this task force pursued plans:

- To identify such community-related aspects of stroke as incidence among the newborn and the frail elderly in localities worldwide;
- To publish a handbook for primary health care workers treating patients with cerebrovascular disease;
- To develop means of restoring maximum functioning to such patients; and
- To implement programs around the world that would reduce the incidence of cerebrovascular disease.

Appointment this year of an internationally noted epilepsy expert as NINCDS Deputy Director spotlighted the Institute's commitment to the scientific conquest of this ailment. The Deputy Director worked with his international colleagues to remove obstacles to cooperative research on the epilepsies. His efforts included:

- Participating in the Third Ecuadorean Congress of Neurology in Quito, delivering four lectures on epilepsy. This Congress is helping to advance neurology in Ecuador from a fledgling discipline to a recognized specialty.
- Working to improve the current classification scheme for epileptic syndromes. This task is being sponsored by the Commission on Classification and Terminology, a group formed by members of the International League Against Epilepsy. When the current classification was published in 1985, some epilepsy experts attacked its usefulness, and the need to draft an improved version became apparent. This year, a work session in Paris produced many recommendations that the League is now reviewing.
- Giving three lectures on epilepsy during a 2-day conference in Mexico City hosted by the Priority Program of Epilepsy. At this conference, a team of Mexican scientists unveiled a potential new antiepileptic compound, which has not yet undergone clinical trials.

To further strengthen the worldwide research attack on epilepsy, the Institute's Deputy Director and scientists from the NINCDS Epilepsy Branch shared information with their colleagues during the 17th International Epilepsy Congress in Jerusalem, Israel. Several of these scientists pursued a special interest in surgical therapies for frontal lobe seizures by participating in a workshop in Esclimont, France.

To share the latest clinical findings from the NINCDS Division of Intramural Research, the Institute's Clinical Director attended the Eighth International Congress of Electromyography and Related Clinical Neurophysiology in Rome. He also participated in two symposia in London, one on Wilson's disease, a disorder that causes the skin to scale and shed, and the other on movement disorders, including Parkinson's disease and dystonia.

Other efforts by NINCDS staff to strengthen international scientific collaborations included:

- Joining with 1 American drug firm and 10 European pharmaceutical companies to fund an international symposium entitled "Descending Brainstem Control of Nociceptive Transmission," which dealt with how neurons relay pain signals. The symposium took place in Beaune, France, and brought together scientists from 16 countries.
- Sharing information about mechanisms of viral pathogenesis during the Seventh International Congress of Virology in Edmonton, Alberta, Canada. Scientists from the NINCDS Laboratory of Molecular Genetics presented material about factors in a host organism that may limit replication of an invading virus.
- Intensifying collaborative work on pain and Alzheimer's disease. Scientists from the NINCDS Division of Demyelinating, Atrophic, and Dementing Disorders discussed the problem of pain with colleagues from 58 other countries at the Fifth World Congress on Pain in Hamburg, Federal Republic of Germany. Another scientist from this Division joined colleagues from 16 other countries to exchange insights about the epidemiology of Alzheimer's disease during a symposium organized by the International Research Group on Dementia of the World Federation of Neurology. This international symposium on Alzheimer's disease met in Amsterdam, Netherlands, and covered such topics as structured diagnostic procedures, pathogenesis, and strategies for treating Alzheimer's disease.
- Attending the Sixth International Catecholamine Symposium in Jerusalem, Israel, where lectures ranged from basic investigations of catecholamine-peptide interactions to clinical studies of catecholamines in relation to cognitive and extrapyramidal function. NINCDS attendees included the Director, Division of Intramural Research, and the Chief, Intramural Experimental Therapeutics Branch.
- Working to improve the quality of epidemiologic surveys done in developing countries. Investigators from the NINCDS Neuroepidemiology Branch and Biometry and Field Studies Branch discussed ways of devising standard research methodologies

with international colleagues attending the Second Pan American Congress of Neuroepidemiology in Santiago, Chile.

Intramural Programs and Activities

The NINCDS Division of Intramural Research contains 8 Branches and 12 Laboratories, many of which engage in international research and sustain collaborative investigations with foreign colleagues working either abroad or in the Institute's laboratories at the NIH.

In the forefront of such efforts is NINCDS involvement in the rapidly expanding field of retrovirus research. The ranks of these slowly incubating viruses include human T-cell lymphotropic virus types I, II, and III—the latter recognized as causing the lethal acquired immunodeficiency syndrome (AIDS). In May 1987, at the NIH campus in Bethesda, Maryland, the Institute hosted an international conference on retroviruses that centered on the newest discoveries and hypotheses in this quickly changing field. The attendees also plotted future research strategies against AIDS.

Laboratory of Central Nervous System Studies: Much of the Institute's work on retroviruses is done through field studies to screen patients with various diseases and to collect sera and other specimens for laboratory analysis. The Laboratory of Central Nervous System Studies conducts crucial international projects, many of which focus on primitive societies in Micronesia, Polynesia, South America, Asia, and Africa. Because of their relative isolation, these societies yield data with fewer of the unknown variables common to highly mobile, cosmopolitan cultures.

Scientists in this Laboratory, working with colleagues in the Institute's Infectious Diseases Branch and Neuroepidemiology Branch as well as with investigators in Colombia and the Seychelles, have demonstrated the etiologic role of a human retrovirus in tropical spastic paraparesis, a widespread degenerative disease of the central nervous system. The scientists found antibodies to HTLV-I in spinal fluid and sera from most patients with tropical spastic paresis in Jamaica, Colombia, Martinique, Trinidad, and the Seychelles. Antibodies to HTLV-I also appeared in Jamaican patients with progressive chronic myelopathy, a steady deterioration of the spinal cord.

Furthermore, antibodies to a virus of the HTLV-I group were found elsewhere in patients with multiple sclerosis, leading the scientists to suspect that the slow viruses cause one disease process to produce varying manifestations—multiple sclerosis in temperate climates and tropical spastic paresis in tropical and subtropical areas.

Scientists from the Laboratory of Central Nervous System Studies have now examined sera from 13 indigenous populations of the southwestern Pacific and have discovered large variations in the prevalence of antibodies to HTLV-I. Antibodies appeared most frequently in sera from populations that have the greatest degree of contact with the outside world.

The Laboratory's investigators also are collaborating with scientists from the Laboratory of Carbohydrate Chemistry in Tokyo, Japan, on a study of the carbohydrate portion of the protein involved in kuru, scrapie, and Creutzfeldt-Jakob disease.

Infectious Diseases Branch: With support from the Agency for International Development, scientists in the Infectious Diseases Branch are collaborating with Egyptian investigators on a study of the causes of congenital central nervous system malformations. Egypt has one of the highest rates in the world of anencephaly and spina bifida. This year, the scientists are continuing a controlled study in Egypt on the effects of prenatal vitamin supplements in reducing the incidence of congenital neurological malformations.

Neuroepidemiology Branch: The Neuroepidemiology Branch has been enlarging the pool of clinical data by tapping existing patient registries, such as the Israeli National Neurologic Disease Registry. Branch scientists also are unearthing new information about risk factors for stroke. They are analyzing intriguing data from a study of stroke cases in the Parsi community of Bombay, India. Preliminary results indicate that the risk of stroke in this community is the same as in the United States, yet the Parsis apparently face fewer risk factors. Three risk factors—hypertension, diabetes, and a history of heart disease—occur in both the United States and India. A fourth risk factor—transient ischemic attack resulting from arteriosclerosis—exists only in the United States. The scientists want to know why the number of stroke risk factors differs while the risk remains the same.

Biometry and Field Studies Branch: Investigators from the Biometry and Field Studies Branch, also working in India, recently finished gathering information about the etiology, treatment, and outcome of head injury cases in New Delhi. The Indian data are being compared with information from patients with similar head injuries in Charlottesville, Virginia. Comparisons of the two groups' morbidity and mortality should

tell investigators whether or not certain treatments merit clinical trials.

Scientists from this Branch and from the Institute's Division of Convulsive, Developmental, and Neuromuscular Disorders are cooperating with colleagues in Yugoslavia on a study to see if electroencephalography (EEG) predicts seizures in children. Together with a team from the Pediatric Clinic in Skopje, the NINCDS scientists are examining nearly 700 children with fever-related seizures. Each child will be monitored with periodic neurological exams and EEG tests.

Laboratory of Neural Control: Scientists from the Laboratory of Neural Control are pursuing five important studies with foreign colleagues. Together with investigators from the Department of Physiology at Queen's University, Kingston, Canada, they are studying the structure and function of complex muscles controlling head and neck movement. This study has relevance to questions about balance and postural control problems and could provide new information about spasmodic torticollis, a disorder characterized by intermittent and uncontrollable twisting of the neck.

Another cooperative venture between this Laboratory and Canadian colleagues is development of an electrically stimulated visual prosthesis to be implanted in the brains of blind persons. The Canadian investigators are from the Department of Neurosurgery at the University of Western Ontario in London. The prosthesis works by intracortical microstimulation, in which the visual cortex receives small electrical impulses. The highly specialized microelectrodes for the prosthesis were fabricated in the Laboratory of Neural Control and will be temporarily placed in the visual cortex of human volunteers undergoing surgery for treatment of epilepsy or tumors. Scientists will then record any perceptions generated.

Laboratory scientists and investigators from the Department of Anatomy at Hebrew University Medical School in Jerusalem, Israel, are examining the interrelationships between neurons and the muscle fibers they stimulate. Together, the nerves and muscles form "motor units" of varying types that may transmit messages differently. Scientists believe motor neuron specialization may play a role in such neuromuscular disorders as myasthenia gravis.

Along with scientists from the Medical Neurology Unit of the John Curtin School of Medical Research in Canberra, Australia, investigators from the Laboratory of Neural Control are studying the arrangement of nerve cells in regions of the brain that control complex voluntary movements. The scientists are looking at how different colonies of neurons transmit messages along the spinal cord to specific muscles or closely related groups of muscles. The investigators want to know whether neurons in the brain fire in patterns that identify muscles and movement commands. In particular, they are looking at how various groups of nerves control arm, wrist, and finger movements.

Scientists from this Laboratory also are collaborating with Japanese gerontologists on a study of the effects of aging on the organization of motor neurons in leg muscles. The Japanese investigators are from the Department of Physiology of the Tokyo Metropolitan Institute of Gerontology. The study should help explain why strength and motor abilities decrease as people age.

During FY 1987, the NINCDS Division of Intramural Research hosted 115 foreign scientists as part of the NIH Visiting Program. The investigators included 19 Visiting Scientists, 21 Visiting Associates, and 75 Visiting Fellows, representing the following countries and areas: Argentina; Australia; Belgium; Brazil; Bulgaria; Canada; Chile; China; Colombia; Czechoslovakia; Denmark; Federal Republic of Germany; Greece; Hong Kong; Hungary; Iceland; India; Iran; Israel; Italy; Jamaica; Japan; Korea; Lebanon; Netherlands; New Zealand; Philippines; Poland; South Africa; Spain; Sweden; Switzerland; United Kingdom; and Taiwan.

Additionally, 19 Guest Researchers, supported by their own countries or nongovernmental sources, worked in NINCDS intramural laboratories during the fiscal year.

Chapter XV
National Institute on Aging

Introduction

The National Institute on Aging (NIA) is responsible for research and training on the biologic, medical, behavioral, and social aspects of the processes of aging and the problems and needs of older people.

The Institute conducts scientific investigations in its intramural research laboratories. The extramural programs support investigators through the competitive NIH peer review system for grants and awards.

Among NIA's priorities is the Institute-wide research effort aimed at Alzheimer's disease, where advances in diagnosis and in understanding the basic mechanisms underlying the disease are being realized. Recently established specialized Alzheimer Disease Research Centers are intensifying work on the etiology of the disease and methods for treatment.

Other areas of importance to the NIA mission include studies of health promotion and research in the social and behavioral sciences which suggest that the productivity of the middle years often can be extended, reversed, or postponed, with nutrition and exercise being important aspects for health maintenance.

Priority areas also include:

- Causes of falls and fractures, particularly osteoporosis and gait and balance disorders;
- Systolic hypertension in older adults;
- Special health needs of racial and ethnic minority populations;
- Demographic and epidemiologic studies of the oldest old (85 years and over), the fastest growing segment of the US population; and
- Continuation of the Baltimore Longitudinal Study of Aging.

In the area of basic science, the newly created NIA intramural Laboratory of Molecular Genetics focuses on the relationship of genes and the aging process and plans to study the molecular basis for the age-dependent decline in immune function, the relationship between aging and cancer, and alterations in the expression of certain genes that may play a role in Alzheimer's disease.

On the extramural side of basic science, the Molecular and Cell Biology Branch focuses on support studies that elucidate the biochemical, physiologic, genetic, and molecular events that lead from gene action to phenotypic expression. The emphases in these four areas are being coordinated to provide a concerted attack on mammalian mechanisms of aging and results to help identify and validate biomarkers of aging.

Highlights of Recent Scientific Advances Resulting From International Activities

An area in which biomedical research accomplishments has been most striking is Alzheimer's disease, one of the Institute's highest research priorities.

Lack of agreement on neuropathologic diagnosis of Alzheimer's disease remains a barrier to research. Some studies suggest that rates of Alzheimer's disease and vascular dementia vary dramatically by nation and ethnicity; for example, there is some evidence that rates of Alzheimer's disease are lower in Japan, China, and possibly certain African nations. This may reflect a genetic predisposition to Alzheimer's disease or environmental risk factors that may vary by culture or region.

An NIA grantee at the University of Western Ontario has produced an international set of quantitative standards for the pathologic diagnosis of Alzheimer's

disease. Although these standards will require further testing in other patient series, they are expected to be a major contribution to the development of research for national as well as cross-cultural comparative studies.

The same grantee also has investigated the neuropathologic findings in Down's syndrome patients. The lesions in older Down's patients with dementia have been known to resemble strongly those in Alzheimer's disease patients. The concentration and location of the lesions may determine the occurrence of dementia in the Down's patient.

Results from a joint project between investigators at the University of California, San Diego, and the University of Lund, Sweden, indicate that brain tissue transplants can reverse learning deficits in severely impaired aged animals. During FY 1987, fetal rat neurons grafted into the brain of an adult rat have been shown to survive and grow when positioned in the host brain in the area normally targeted by the cells. Memory and learning function can be improved in impaired adult rats by the grafting of fetal cholinergic neurons from the basal forebrain into the hippocampus. This work demonstrates the efficacy of basic animal transplant research to study brain mechanism, which may be important in human disease. Such fundamental investigations in the plasticity of the brain are important to advancement of research in the United States and elsewhere, because they can be applied to improve understanding and treatment of dementia and related neurologic disorders in the human population.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

Israel: Planning for the November 15–17, 1987, U.S.-Israel Binational Symposium on the Challenge of Aging Societies was undertaken during this period. This symposium, the fourth in the series of U.S.-Israel binational symposia, will be co-sponsored by the Office of International Health, Public Health Service, and NIA under the Agreement for Cooperation in the Field of Health. Joint presentations will be made on the following topics:

- Needs and approaches to the health of the elderly;
- Epidemiology of aging in relation to planning of services;
- Education of health care providers for care of the elderly; and
- Clinical challenges in aging, particularly the combination of clinical and functional approaches.

The following issues will be addressed in concurrent workshops:

- Alzheimer's disease and other dementias;
- Forecasting the care needs of the elderly: methodology and limitation;
- Health promotion in the elderly;
- Hospital, community, and informal care of the elderly; and
- Resources for research in aging: special populations, longitudinal studies, tissue banks, and research personnel.

The proceedings of the symposium are expected to be published in *Public Health Reports* and a comparable Israeli journal.

Italy: As a continuation of the Memorandum of Understanding between the DHHS and the Italian Ministry of Health, under the umbrella of the U.S.-Italy Science and Technology Agreement, a joint conference is being planned to explore collaboration on epidemiologic studies on aging. The topics to be addressed are:

- Demographic profiles;
- Development of standards;
- Role of longitudinal studies;
- Diagnostic issues;
- Risk factors;
- Metabolic, neuroendocrine, and immunologic studies; and
- Care and treatment.

The potential of a joint project capitalizing on the data from the NIA New Haven and East Boston Established Populations for Epidemiological Studies of the Elderly (EPESE) also will be explored. The project would involve comparative studies of Italian migrants in these U.S. regions with nonmigrant relatives who remained in Italy.

Japan: Active collaboration continues between the Tokyo Metropolitan Institute of Gerontology (TMIG) and NIA. Scientist exchanges have led to joint research projects. The first joint symposium, held February 18–19, 1987, at TMIG, focused on age-related changes in calcium function. The University of Michigan and NIA also co-sponsored the opportunity for TMIG social and behavioral staff to receive meth-

odologic research training and to participate in research projects in the United States.

The Fourth Japan-U.S. Conference on Aging, held in Tokyo September 15–19, 1986, was organized by representatives of the Nihon University, TMIG, and the East-West Center in Hawaii. The objectives of this conference, which focused on the quality of life of elderly people, were to clarify and promote the development of comparative studies of this population's health problems and social factors.

Activities With International and Multinational Organizations

Agency for International Development: The FY 1987 Senate Report accompanying the Foreign Assistance Appropriations Bill (S. 2824) recommended that the Agency for International Development (AID) set aside at least $5 million for international research on problems affecting older persons. AID was directed to collaborate with NIA in activities such as comparative international epidemiologic studies on Alzheimer's disease and related dementias, osteoporosis, and other health problems that affect older people.

As a result of meetings between NIA and AID staff, several activities are now under way. These include:

- Expansion of the Bureau of the Census International Database from 31 countries, 6 of which were less developed nations, to include 22 additional less developed countries;
- Travel for one scientific expert from Israel and one from Australia to participate in the 1987 Public Health Conference on Records and Statistics held in Washington, D.C., July 13–15. The conference was co-sponsored by NIA and the National Center for Health Statistics; its theme was "Data for an Aging Population," and initiatives in demographic and epidemiologic research in cross-national aging were addressed; and
- Support for the WHO-NIA planning initiative for the establishment of the WHO Special Program for Research on Aging.

During this period, AID used a Kellogg Fellow to help the agency develop a research agenda on aging in the developing world, sponsor seminars on the aging world for AID staff, and prepare a report for the Agency's consideration.

In addition, the agency has announced plans to employ experts on social and economic conditions in AID-assisted countries to work with AID and NIA on issues of aging and to convene a special meeting on aging in the developing world. AID has allocated $200,000 for this planning phase. NIA and AID will continue to explore mutual endeavors during FY 1988.

World Health Organization: The Memorandum of Understanding between the World Health Organization (WHO) and the NIH to establish the implementing unit for the WHO Special Program for Research on Aging (SPRA) at NIA was signed June 16, 1987. The newly appointed Chief of this WHO Unit, together with cooperating staff of NIA, is undertaking the initial planning phase for this coordinated multinational research effort. The scientific areas of concentration, as identified by the WHO Global Advisory Committee on Health Research, will include:

- Epidemiology and determinants of healthy aging;
- Age-related dementias;
- Immune function and aging; and
- Nutritional aspects of osteoporosis.

As with other WHO Special Programs, the primary support for research projects and related activities, such as training, will derive from extrabudgetary funding, which will be sought through a special invitational meeting in Geneva for potential donors in July 1988.

During FY 1987, NIA staff also participated in a WHO-sponsored symposium on consensus development in the diagnosis of Alzheimer's disease. The proceedings of this symposium will be published in a volume co-edited by the NIA Associate Director for Neuroscience and Neuropsychology of Aging.

Extramural Programs

Table XV–1 shows NIA-funded grants to investigators in institutions outside the United States during FY 1987.

Table XV–1

NIA GRANTS TO FOREIGN INSTITUTIONS, FY 1987

Recipient	Title of Project
Israel	Study of Faulty Protein Molecules Senescence
Canada	Definition of Alzheimer's Disease: Pathological Studies
Israel	Retirement, Coping and Health: A Retirement Study
Canada	The Aged and Answering "Why" Questions About Memory
Israel	Error Prone Repair, Mutogenesis and Aging
Canada	Video Recording of Falling in the Elderly
Canada	Balance Test to Depict Falling in the Elderly
Canada	Model for Lipofuscin Accumulation in Aging and Disease

In addition to these, Table XV–2 shows grants to domestic investigators and a contract that contains foreign components involving the countries cited.

Table XV–2

NIA GRANTS TO U.S. INVESTIGATORS, FY 1987

Country Involved	Title of Project
Netherlands	Aging Changes in Neuronal Function and Structure
Ireland/Botswana	Age and Culture: Community and Well-Being in Old Age
Sweden	Genetic and Environmental Influences in Behavioral Aging
Israel	Individual Aging
United Kingdom	Alzheimer's Disease Research Center: The Efficacy of THA in Alzheimer Disease
Japan	Self-Care Behaviors of Aged Japanese
Sweden	Embryonic Nerve Cell Transplantation in Aged Rat Brain
Japan	Well-Being Among the American and Japanese Elderly
China	Impact of China's Economic Reforms on the Elderly
Luxembourg	Comparative Economic Status of the Elderly
31 countries	Development of an International Data Base on Aging/U.S. Bureau of the Census

Biomedical Research and Clinical Medicine Program: Highlights of extramural grants activities during 1987 include a project by a Canadian investigator on age- and disease-related changes in bone mineralization. These studies, supported by the NIA Geriatrics Branch, have used a variety of mammalian species, including human subjects. The findings on normal bone are being used as a basis of comparison to examine changes that occur in pathological conditions such as osteoporosis, osteopenia, osteomalacia, and rickets. Thus far, it has been learned that the mineral fraction of bone becomes more dense in immobilized species than in controls. Although castration has no effect on the bone mineralization of one species of aged animal model, the bone density of another estrogen-treated species was found to increase. Also, dietary fluoride does not change in chemical composition of bone, but in rat species, there is a shift to more dense bone over time.

One of several foreign projects supported by the Molecular and Cell Biology Branch suggests that erythrocyte turnover is more rapid in older individuals. Antibodies produced against four purified protein components will be used to screen for oxidative damage to and degradation of these proteins.

Neuroscience and Neuropsychology of Aging Program: The Neuroscience and Neuropsychology of Aging Program is now drafting a Program Announcement to solicit proposals on international and cross-national investigations of the epidemiology of Alzheimer's disease. The purpose of these investigations will be to learn more about:

- Age-specific incidence rates of this disease as they vary by geographic, racial, ethnic, socioeconomic, or cultural characteristics;
- The natural history of Alzheimer's disease;
- The determinants of duration and life expectancy; and
- The immediate, pathologically verified causes of death of Alzheimer's victims and how the cause-of-death distribution varies cross-nationally and cross-culturally.

Behavioral and Social Research Program: Two conference grants supported by the Behavioral and Social Research Program have resulted in publications. One deals with China and the relationship among long-term population aging, population planning, the family, and collective efforts for providing health, economic, and social support in old age. The other publication focuses on migration of the elderly. Staff of this program also are involved with an international network of researchers who are interested in developing new health promotion indicators. Activities in this area will lead to publication of "Measuring Health Behaviors and Health," a special supplement to *Health Promotion: An International Journal.*

The Economics, Demography, and Population Branch of the Behavioral and Social Research Program is incorporating a variety of international perspectives in its program development. These include further expansion of the Bureau of Census International Database on Aging, by adding countries, including a new focus on developing nations, and adding health and care utilization data. Two reports on this International Database on Aging are to be released: "An Aging World," summarizing detailed demographic and socioeconomic statistics that have been collected in 31 countries and "Population Aging in the Third World," describing the dramatic demographic changes that less-developed countries are expected to experience. In addition, planning is under way for:

- A United Nations international demographic yearbook on the elderly and mapping of physical functioning and health in developing countries;
- Trajectories of functioning in the oldest old;

- A conference on population aging in developing countries that would relate to the development of a theoretical base of demography of aging; and
- A series of Program Announcements or Request for Announcements in the area of population aging in developed and developing countries.

International Conferences, Seminars, and Meetings

NIA staff travel outside the United States often is precipitated by invitations to consult, lecture, and/or present scientific papers. These activities help staff keep current with the state of the art and the advancement of science worldwide. The Institute also hosts experts from around the world for advice in program planning and development in given areas of research pursuits.

From time to time, the Institute co-sponsors symposia with organizations outside the United States. For example, in April 1987, the Ciba Foundation (United Kingdom), the Fogarty International Center, and NIA co-sponsored a workshop on research and the aging population, the proceedings of which are published and available through the Ciba Foundation. The workshop topics included:

- The health of the elderly population and results from longitudinal studies with age cohort comparisons;
- Health and aging in the developing world;
- Aging and disease;
- Cerebrovascular disease and the elderly;
- Alzheimer's disease;
- Questions in old age psychiatry;
- Cardiovascular disease in the elderly;
- Disorders of the skeletal system in the elderly;
- Aging and infection;
- Malignant disease and the elderly;
- Longitudinal insights into the aging population;
- Models of aging;
- Changing health needs of the aging population;
- Planning for health services for the elderly; and
- Distributing the cost for long-term care.

In June 1987, the NIA Director represented the United States in the Kellogg Foundation Work Group on Multidisciplinary Health Assessment of the Elderly, held in Goteborg, Sweden. Other participating countries included Canada, Denmark, France, Italy, Sweden, Switzerland, and United Kingdom. The group arrived at a consensus on conclusions and recommendations for the place and nature of multidisciplinary assessment in the care of older persons at critical points in their lives as well as directions for further research and development. The summary of the proceedings was published in a special issue of the *Danish Medical Bulletin.*

Intramural Programs and Activities

Basic biomedical, physiologic, and psychological studies, conducted in NIA research facilities in Baltimore and on the NIH campus, attract scientists and national health representatives worldwide.

The intramural laboratory research program hosted lecturers and visitors from China, France, Hungary, Israel, and Japan during FY 1987. These included a delegation from the Japanese Ministry of Health and Welfare and investigators from the Japan Institute for the Control of Aging, Otsuka Pharmaceuticals, and the Japanese National Center for Neurology and Psychiatry. Members of the French Association for Gerontology, a geriatrician from Hospital George Clemenceau in Paris, and a librarian from the Brookdale Institute of Gerontology in Rehovot, Israel, were also among those who toured and met with staff of the NIA intramural program.

During FY 1987, 63 Visiting Fellows and Scientists contributed to 39 separate intramural research projects.

These included two scientists from France and Japan, working in the Laboratory of Biological Chemistry on the regulation of mineral metabolism and the pathophysiology of osteopenia in aging rodents. An investigator from Mexico, working in the Laboratory of Cardiovascular Science, is involved in studies to assess the physiologic importance of calcium ions in the regulation of energy metabolism. In the same Laboratory, a Japanese researcher is working in tandem with other Gerontology Research Center (GRC) investigators measuring the structure and function of cardiac myocytes in rats of various ages. A Visiting Scientist from Poland is working with staff of the Endocrine Section on pituitary and hypothalamic function in experimental animals of different ages. With staff of the Laboratory of Molecular Genetics, a scientist from India is investigating whether or not age-dependent alterations exist in the abilities of human cells to repair DNA damage.

Other foreign collaborative studies include joint research projects with investigators in:

- The Max Planck Institute in Frankfurt, Federal Republic of Germany, on kinetics of the Na,K-ATPase partial reactions;
- University La Sapienza, Department of Medicine, Rome, Italy, on regulation of interleukin 2 gene expression in lymphoid and nonlymphoid cells;
- Nihon University, School of Dentistry, Tokyo, Japan, on bone mineral density and osteoporosis;
- Institute for Medical Research and Occupational Health, Zagreb, Yugoslavia, on cross-cultural studies in normative aging and osteoporosis; and
- Kyoto University, Japan, on age dependent expression of viral genes.

Collaboration with foreign investigations also is important in the Laboratory of Neurosciences. An investigator from Canada is providing pathological diagnoses of brains of patients who have died of dementia of the Alzheimer type. This same investigator also is participating in the Laboratory's clinical program involving positron emission tomography. The measurements provided by this collaboration are then correlated with the Laboratory's premorbid measurements of cerebral metabolism and cognitive functioning.

The international interests of the Epidemiology, Demography, and Biometry Program are primarily in comparative studies of aging in similarly derived ethnic groups in differing environments. Scientific opportunities exist for studies comparing the health of participants in the U.S. Established Populations for Epidemiological Studies of the Elderly with populations outside the United States, such as in developed and developing countries in and around the Pacific Basin. Also under consideration are opportunities for involvement in research on dementia and other diseases of aging among individuals of Japanese ancestry in Japan and in the United States.

This program occasionally hosts Guest Researchers from other countries. During FY 1987, an expert from the Netherlands was engaged in a project concerning the elderly persons in the U.S. National Health and Nutrition Examination Survey I, analyzing data relating characteristics at baseline to vital status after approximately 12 to 14 years of followup. For this project, a grant was obtained from the Netherlands Organization for the Advancement of Pure Research.

Chapter XVI
National Library of Medicine

Introduction

The international programs of the National Library of Medicine (NLM) are integral to NLM's responsibilities in biomedical information. The programs are based on cooperative undertakings and are a natural extension of domestic functions.

Highlights of Recent Scientific Advances Resulting From International Activities

During the past year, NLM has continued its bilateral cooperative MEDLARS agreements with individual countries and its cooperation with international governmental organizations such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO) and international nongovernmental organizations such as the International Council for Scientific and Technical Information (ICSTI). The Special Foreign Currency Program was active in the production of critical reviews and history of medicine projects. Other NLM international activities have included specialized training for foreign colleagues, the NLM publications exchange program, and visits from numerous professionals from abroad.

Summary of International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

The National Library of Medicine has MEDLARS agreements with partners in 15 foreign countries and with PAHO. Table XVI–1 describes services provided in the International MEDLARS Centers:

India has shown an interest in sharing advances in science and technology with NLM. There were discussions with a science and technology delegation from India and with the Minister of Health about creating a MEDLARS Center in New Delhi. The Indian Government has since decided to nominate the National Informatics Centre (NIC) as the organizational entity to serve as a MEDLARS Center.

In early 1987, two members of the staff and the Director of the National Informatics Centre visited NLM for additional technical and economic information. It is anticipated that limited online access will begin at NIC in New Delhi. NIC has plans to develop software to run MEDLINE service in India.

Activities With International and Multinational Organizations

The National Library of Medicine has enjoyed 20 years of collaborative activities with the Pan American Health Organization. The PAHO Regional Medical Library (BIREME) in Sao Paulo, Brazil, provides MEDLINE service to users in Latin America and the Caribbean countries. PAHO has instituted online access for major medical schools in Chile, Costa Rica, and Jamaica.

NLM continues to cooperate with the World Health Organization to produce the *Quarterly Bibliography*

Table XVI–1

SERVICES PROVIDED IN INTERNATIONAL MEDLARS CENTERS

Tapes	Tapes/Software	Online NLM
France	Australia[a]	BIREME (PAHO)[a]
Germany, Fed. Rep.	China	Canada
Japan	Sweden	Colombia
BIREME (PAHO)		Egypt
		France[a]
		Italy
		Kuwait
		Mexico
		South Africa
		United Kingdom

[a]Combined online/tapes.

of Acute Diarrhoeal Diseases. NLM searches the literature, classifies the articles retrieved, and prepares camera-ready copy; WHO prints and distributes the bibliography to thousands of institutions in developing countries. The Library also supports the *Quarterly Bibliography of Major Tropical Diseases,* printed in India and distributed internationally by WHO. NLM provides MEDLINE bibliographies in camera-ready form to PAHO, and PAHO prints and distributes these in the *Bibliography of Respiratory Infections in Children.*

NLM and WHO also continue a collaborative arrangement to provide photocopies of journal articles for the use of health professionals in developing countries in Africa, the Eastern Mediterranean, and Southeast Asia. Library resources in developing countries are usually insufficient, and the need for biomedical and health information can be met only by drawing on the collections of the developed world. Even though NLM provides approximately 3,000 photocopies a year to developing countries, this number can only partially meet their demand. Unless other resources in developed countries can be found, the need for interlibrary loans to developing countries will continue to grow.

Extramural Programs

NLM's Special Foreign Currency Program (SPFC) (authorized under P.L. 480) employs U.S.-owned local foreign currencies to support biomedical scientific publications useful to U.S. health professionals. This program is administered in the International Programs Branch of the Extramural Programs Division.

A great number of SPFC projects active during the past year were research monographs and translations of classics in the history of medicine; state-of-the-art critical reviews and monographs that analyze research and practice in biomedicine; translations into English and printing of foreign medical studies; and secondary literature tools such as bibliographies and biomedical guides.

Among the new studies in NLM's Resources in Medical History Series, to be published in India during this fiscal year, were an English translation of *On Insanity and Its Classification,* Vincenzo Chiarugi; *Johannes Muller and the Nineteenth Century Origins of Tumor Cell Theory,* L.J. Rather, et al.; and *Body Posture,* R. Magnus.

Two reprints of notable historical studies in English also were published through the Indian program in FY 1987: *The Mechanical Factors of Digestion,* Walter B. Cannon; and *A Treatise on the Management of Pregnant and Lying-in-Women,* Charles White.

International Conferences, Seminars, and Meetings

NLM held an invitational workshop that was sponsored jointly with the Fogarty International Center, the Division of Computer Research and Technology, and the Division of Research Resources. For 2 days, 45 participants from 22 developing countries met to exchange their viewpoints and experiences in international collaboration on the application of medical informatics. One consensus reported by participants was that microcomputers reach more households in the United States and other developed countries, but that computer use in medicine in developing countries was not progressing at the same pace. The opinion was that unless international collaboration and national resources for medical informatics are developed rapidly, the gap between the developed and developing countries will not be narrowed.

NLM is a member of the International Council for Scientific and Technical Information. This organization serves as a meeting ground for information and abstracting agencies, commercial and governmental, in a number of countries around the world. Common interests include:

- Economics of primary and secondary publications;
- Transborder flow of information;
- Electronic publication;
- Standardization; and
- Information needs for developing countries.

At the 1987 general meeting of ICSTI held in New York City, NLM was represented by the Director for International Programs.

Intramural Programs and Activities

NLM continues to attract hundreds of foreign visitors each year, including doctors, medical librarians, public health specialists, and governmental officials. Many of these visitors have responsibilities for medical, scientific, or technical information in their own countries. Their interest in NLM is more than cursory, and they are officially received and briefed on relevant aspects of NLM operations and research. In FY 1987, visitors came from the following countries and areas: Australia; Belgium; Bulgaria; Chile; China; Congo; Costa Rica; Czechoslovakia; Denmark;

France; Federal Republic of Germany; Honduras; Hong Kong; Hungary; India; Iraq; Ireland; Italy; Ivory Coast; Jamaica; Japan; Korea; Kuwait; Malawi; New Guinea; New Zealand; Pakistan; Peru; Portugal; Singapore; South Africa; Sweden; Trinidad; Upper Volta; United Kingdom; U.S.S.R.; Venezuela; Yugoslavia; Zaire; West Indies; and Taiwan.

Many official delegations came to scrutinize the Library's operations and to discuss technical issues with NLM staff, usually with a view to identifying applications that might prove useful. In addition to foreign visitors, NLM received many trainees, students, and professionals in observer roles for short periods.

Chapter XVII
Warren Grant Magnuson Clinical Center

Introduction

More than 30 years ago, the Warren Grant Magnuson Clinical Center (CC) was authorized by Congress to provide the quality patient care necessary to conduct biomedical research. The 540-bed hospital has facilities and support services for nearly 1,000 physicians who conduct clinical research for 9 of the 12 NIH Institutes and for the National Institute of Mental Health (NIMH). It was specially designed to place patient care facilities close to research laboratories to promote the quick transfer of new findings of basic and clinical scientists to the treatment of patients. Institutes admit to their units only those patients (upon referral by personal physicians) who have the precise kind or stage of illness under investigation by scientist-clinicians.

The Warren Grant Magnuson Clinical Center is staffed and equipped to:

- Ensure the highest possible level of medical care to each patient;
- Provide optimal resources and facilities for clinical research;
- Perform research on methods and systems involved in patient care and study;
- Disseminate information to professionals and to the public relevant to clinical investigation;
- Develop and maintain training programs in the techniques and ethics of biomedical and clinical research; and
- Interact with scientists and physicians, nationally and internationally, on mutual problems of clinical research such as policy, education, ethics, and priorities.

CC departments are responsible for hospital services, except for direct physician care, and conduct research in their own specialties.

Nuclear Medicine Department

The Nuclear Medicine Department of the Clinical Center provides diagnostic and research services to various NIH institutes. The Department has made major strides in implementing new collaborative research focusing on positron emission tomography (PET) and the application of radiolabeled monoclonal antibodies to diagnostic imaging and immunotherapy.

With PET, the Department combines computer technology with procedures using molecules labeled with radioisotopes that emit positrons, electrons that are positively charged. The radioactivity is detected by the sophisticated PET scanners, which display and image the organs being studied. The PET imaging technique has an advantage over other imaging techniques because PET images reflect not only the anatomy of organs but also their function. The Department has recently undergone major physical renovations and acquired new pieces of equipment for the purpose of rapidly producing short-lived radiopharmaceuticals for PET studies. Two state-of-the-art PET scanners also have been installed, giving the NIH one of the largest capacities for PET scanning in the world.

The Nuclear Medicine Department also has been successful in using radioactively labeled monoclonal antibodies to selectively highlight diseased tissue in the body and provide precise information on the exact location and extent of disease. Monoclonal antibodies work much like puzzle pieces fitting together chemically, because the antibodies have a high affinity for certain molecules in the body called antigens. Standard nuclear medicine scans are then used to locate the radioactively labeled antibodies, and any abnormalities in the images indicate areas of diseased tissue. This technique is considerably more sensitive than standard scans and can highlight very minute areas of diseased tissue, such as tumor or heart tissue.

Department of Rehabilitation Medicine

The Department of Rehabilitation Medicine, Clinical Center, provides state-of-the-art consultation and treatments to NIH patients. In addition, it conducts original research and collaborates in many Institute research protocols. An important research mission is the development of new methods for delivering rehabilitation therapies and designing new devices and aids to improve rehabilitation outcome. The Department has one of the world's most sophisticated motional analysis laboratories and is developing new orthotics and clinical assessments of biomechanical function.

Several international scientists toured the Rehabilitation Medicine Department and Motion Analysis Laboratory this year, and a National Institute of Neurological and Communicative Disorders and Stroke Guest Researcher from Beijing, China, spent time observing up-to-date rehabilitation techniques.

The Chief of the Department of Rehabilitation Medicine presented a talk at St. Joseph's Hospital, London, Ontario, on psoriatic arthritis. The Chief and Deputy Chief were invited to participate in a delegation of U.S. rheumatologists to China to exchange current information on arthritis management. (Funding problems prevented their acceptance.)

The Chief of the Physical Therapy section attended the 10th International Conference of the World Confederation for Physical Therapy, Sydney, Australia, in May, 1987. He presented a paper entitled "Consideration for the Physical Therapist in the Treatment of the Oncologic Patient in the Year 2000."

Department of Transfusion Medicine

The Department of Transfusion Medicine's international program activity has been limited in scope and has focused primarily on information exchange through organized symposia. In addition, it sponsored two Visiting Fellows from China who are currently engaged in research investigations of hepatitis viruses. The Department participates in an ongoing scientific exchange with Japan and co-sponsors an international symposium on viral hepatitis, which takes place every 3 years. During FY 1987, members of the Department have been invited to speak in Austria, China, Federal Republic of Germany (FRG), Japan, Netherlands, and United Kingdom.

A Visiting Fellow from China is engaged primarily in the investigation of a new infectious agent isolated from acquired immunodeficiency syndrome (AIDS) patients with Kaposi's sarcoma. He is responsible for the development of serologic tests for the agent and for determining immunoresponse in experimentally infected animals. He also participated in the identification and evaluation of the cloned gene fragments of this agent. The same scientist assisted in the development of an alternative assay to detect antibody to hepatitis B virus core antigen. This assay is of importance in the screening of blood donors for both the hepatitis B and virus (HBV) non-A, non-B hepatitis agents.

Another Visiting Fellow from China participates in the laboratory's ongoing research of hepatitis B virus, specifically to evaluate the immunoresponse of HBV-infected humans to the epitopes located in the pre-S region of hepatitis B surface antigen. This scientist also will be responsible for studies evaluating the biophysical nature of the non-A, non-B hepatitis agent.

The Blood Services Section of the Department of Transfusion Medicine has been collaborating with the Asahi Medical Company of Japan to evaluate a new automated filtration system to permit rapid collection of large volumes of donor plasma. The system appears to be both safe and effective.

The Chief of the Department of Transfusion Medicine was a keynote speaker at a meeting of the Japanese Society of Apheresis held in Tokyo.

The Chief of the Blood Services Section was an invited speaker at the 35th annual meeting of the Japanese Society of Blood Transfusion and at the Japan Society of Blood Component Therapy meeting, both held in Tokyo, Japan, in March 1987. She also was an invited speaker to the 11th Annual Symposium on Blood Transfusion, sponsored by the Netherlands Red Cross and held in Groningen, Netherlands.

The Chief of the Immunology Section gave a plenary session lecture on non-A, non-B hepatitis at the International Hepatitis Symposium in London, England. He also addressed the German Society for Transfusion Medicine and Immunohematology at a meeting held in Innsbruck, Austria. At this gathering, he discussed anti-hepatitis B core testing for the prevention of non-A, non-B hepatitis, a test that FRG and Austria are considering implementing, as the U.S. has recently done. He also spoke in Munster, FRG, on the topic of viral inactivation for the prevention of transfusion-associated hepatitis.

The Chief of the Transfusion-Transmitted Viruses Section presented two posters at the International Hepatitis Symposium in London, England. He gave talks in the following cities of China: Shanghai, Hungzhou, Zhengzhou, and Beijing. His topics were transfusion AIDS, non-A, non-B hepatitis, and structural-functional relationship of HBV. He also continues to collaborate with the chairperson of the Microbiology Department, Shanghai Medical University. Their common interest is in hepatitis B infection and its immune response.

Chapter XVIII
National Center for Nursing Research

Introduction

The National Center for Nursing Research (NCNR) was authorized under the Health Research Extension Act of 1985, P.L. 99-158. On April 18, 1986, the Secretary of the Department of Health and Human Services announced its establishment as part of the National Institutes of Health. NCNR's mission is the conduct and support of, and dissemination of information respecting basic and clinical nursing research, training, and other programs in patient care research.

The research programs of NCNR address actual and potential health problems, focusing on:

- Health promotion and disease prevention;
- Understanding and mitigating the effects of acute and chronic illnesses and disabilities;
- Delivery of nursing services; and
- Ethics of patient care.

Nursing research examines the biologic, biomedical, and behavioral processes that underlie health and the environment in which health care is delivered.

Summary of International Programs and Activities

NCNR has not yet developed an international program in nursing research. It is expected that within the next 2 years, NCNR's research and research training activities will be expanded to encompass an international program.

International Conferences, Seminars, and Meetings

In FY 1987, three NCNR staff members participated in the International Research Congress held in Edinburgh, Scotland, July 29-30. Staff activities included a presentation of a paper on nurse turnover, sponsorship of a poster session on perception of infant needs, and conduct of a seminar on the purpose, organization, and scope of NCNR program activities. In addition, NCNR staff interacted with nurse researchers from many countries for a mutual exchange of information on nursing research in the respective countries. The congress was co-sponsored by Sigma Theta Tau International Honor Society of Nursing; the Department of Nursing Studies, University of Edinburgh; and the Royal College of Nursing Research Society, United Kingdom.

Chapter XIX
Division of Computer Research and Technology

Introduction

The Division of Computer Research and Technology (DCRT) has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of the NIH. DCRT serves as a scientific and technological resource for other parts of the Public Health Service and for other Federal organizations that have biomedical and statistical computing needs. It is the goal of DCRT to ensure that scientists and administrators can fully explore advances in computing technology.

Since its founding in 1964, DCRT has grown to become the largest biomedical computing facility in the world. Its staff members continue to create still more powerful and useful systems and to seek new ways to bring computers, mathematics, and engineering into the service of science and to enhance administrative effectiveness.

Highlights of Recent Scientific Advances Resulting From International Activities

Until recent years, there has been little direct information about molecular forces in aqueous media. In particular, the role of the water surrounding two interacting molecules has been especially difficult to define.

In a collaborative study, researchers have developed an osmotic stress method for directly measuring the force required to push electrically neutral lipid membranes. They have identified very strong repulsive hydration forces between membranes even separated by 20 to 30 Angstroms, that is, some 7 to 10 molecular diameters of water. This force easily dominates all other interactions, even electrostatic forces in the case of electrically charged interacting membranes. Hydration barriers in this range of separations have been found to be virtually ubiquitous among membranes and are an important factor in maintaining stable membrane structure. The loss of this repulsion in living systems, as when membranes are destined to fuse, is a closely regulated event that involves deliberate changes in membrane structure, composition, and ionic environment.

A Yugoslav physicist, now at the Australian National University, showed how water several layers away from the molecular surface can be influenced by the first layer of water in direct contact with the surface.

Summary of International Programs and Activities

Extramural Programs

DCRT staff members collaborated with scientists from foreign countries, including Canada, France, Japan, Netherlands, Spain, and Yugoslavia. Examples of international collaborative activities include the following:

- Instrumental analysis;
- Correlation function spectroscopy/neutron light scattering;
- Mathematical and statistical studies;
- Representation of protein folding processes;
- Representation of protein modules as elements for protein design;
- Molecular forces in cellular assembly; and
- Cell membrane fusion studies.

Visitors to DCRT throughout the year included scientists and researchers from India and Mexico.

International Conferences, Seminars, and Meetings

The DCRT Director served on the organizing committee of MEDINFO '86, the fifth world congress on

medical informatics, which was held in Washington, D.C., October 26–30, 1986.

These congresses, presented by the International Medical Informatics Association, have been held previously in Stockholm, Toronto, Tokyo, and Amsterdam. They are sponsored by a nonprofit corporation composed of 12 leading U.S. medical and engineering societies. The goal of MEDINFO is to promote medical and health care computing in all countries of the world.

Three DCRT members of the NIH-wide Image Processing Group participated in a video teleconference for DOCUMED-Europe '87, held in Amsterdam, Netherlands, in May. DOCUMED was established to initiate a common forum in which physicians, audiovisual professionals, and decisionmakers from every field of the medical profession could examine imaging technologies and their applications in medicine.

Intramural Programs and Activities

Visiting Scientists from India, Israel, and Japan worked in DCRT during FY 1987. Research projects included:

- Molecular graphics, computer modeling, and sequence analysis;
- Modeling of the beta receptors; and
- DNA sequence analysis and related methods.

Chapter XX
Division of Research Resources

Introduction

The Division of Research Resources (DRR) sponsors international activities through its Regional Primate Research Centers Program and grants made to several of the Regional Primate Research Centers. International cooperation offers access to nonhuman primate resources and opportunities that contribute to the achievement of center research and resource objectives and that frequently are available only in foreign countries.

Highlights of Recent Scientific Advances Resulting From International Activities

A staff scientist at the Wisconsin Regional Primate Research Center has played a key role in the formal establishment of Korup National Park in Cameroon this year. He has served as scientific advisor for the Korup project for the past decade. Some 14 primate species, several of which are of importance to biomedical research, are found in the park. This scientist's ecological work is helping to ensure the conservation and preservation of these and a number of other valuable plant and animal species. It also provides a protected field site where long-term observational studies can be performed.

A consortium composed of the Washington and Oregon Regional Primate Research Centers and the Bowman-Gray School of Medicine formally completed an agreement with Indonesian counterparts, including the Minister of Population and Environment, to establish a nonhuman primate natural habitat breeding project in Indonesia. The project will be located on a coastal island and produce retrovirus-free cynomolgus monkeys needed for research on acquired immunodeficiency syndrome (AIDS). The agreement, which provides for the training of Indonesian veterinarians, is in response to requests from the Indonesian Government for more substantive U.S. involvement in nonhuman primate conservation activities. A more solid base for conducting research on Indonesian health problems that requires the use of nonhuman primates also will be created.

Summary of International Programs and Activities

Extramural Programs

Staff in the Parasitology Department of the Delta Regional Primate Research Center are continuing to participate in a field research project in Haiti on filariasis. This project is supported primarily by an International Center for Infectious Disease Research grant to Tulane University from the National Institute of Allergy and Infectious Diseases. The DRR grant to the Delta center supports the salary of the participating center scientists. Although largely a long-term epidemiologic study of filariasis, there are laboratory components to the work. Nonhuman primates (primarily patas monkeys, *Erythrocebus patas*) are susceptible to infection with *Wuchereria bancrofti* and *Brugia malayi* and are important as well-characterized sources of microfilaria that are used in mosquito feeding and other laboratory studies. This work earlier resulted in the discovery that nonhuman primates could be infected experimentally with *Mansonella*, another form of filarid parasite that was thought to infect only humans. The Haitian project also provides a source of *Plasmodium falciparum*, a malaria parasite, which is the target of sponsored work at the center that depends on the use of squirrel monkeys for malaria drug and infectivity studies.

The Indonesian Natural Habitat Breeding Project was launched this year with DRR grant support to the Washington Regional Primate Research Center and contributions from 14 other Federal agencies represented on the Interagency Research Animal Com-

mittee. The three institutions in the Indonesian consortium are providing 1 year of training in the United States for three Indonesian veterinarians, who will return to provide the professional expertise necessary to manage the project locally.

Ecological studies in Korup National Park, Cameroon, are supported by a DRR grant to the Wisconsin Regional Primate Research Center, which primarily funds the scientific advisor's salary. Rain forests throughout the world are being destroyed rapidly, and few such forests remain intact in Africa west of Korup. Even fewer maintain their original flora. Korup has a rich diversity of species and is high in endemic species of flora and fauna. One-quarter of Africa's nonhuman primate species are sheltered in Korup, which provides a unique resource for both conservation and research on African nonhuman primates and interrelated human health problems.

Support has been provided to the Institute for Primate Research in Kenya for some time through the DRR grant to the Yerkes Regional Primate Research Center. These funds have helped to provide the director's salary. With additional support from a number of other sources, the institute has developed into an exemplary resource for biomedical research in Africa that requires the use of nonhuman primates. The institute also is a valuable resource for supporting laboratory and field studies in Kenya, which are conducted in cooperation with visiting U.S. scientists, among them members of the Yerkes staff. Supplemental funding this year to Yerkes will support the training of an institute virologist in the United States and the conduct of field surveys in Kenya for retroviruses that occur there in nonhuman primates. The virologic capabilities that are planned for the institute and the proposed studies may yield new nonhuman primate models for AIDS and improve understanding of the ecology of the retroviruses that cause immune deficiency diseases in animals and humans.

Chapter XXI
Division of Research Services

Introduction

Through cooperation and collaboration with national and international organizations, the Division of Research Services (DRS) plans and conducts centralized programs of scientific, engineering, and technical services in support of biomedical research activities. Professional and technical staff members consult with research scientists during all stages of a research project on the development and use of essential products and services.

DRS personnel:

- Provide specialized assistance and services in biomedical engineering and instrumentation design and development;
- Furnish research animal production, maintenance, procurement, and disease identification and control;
- Provide biomedical library and translation services; and
- Make available specialists in medical arts and photography.

DRS personnel are involved internationally in such activities as:

- Conducting collaborative exchange in research projects in instrumentation and biomedical engineering;
- Serving on boards of scientific counselors for national research organizations in foreign countries;
- Establishing collaborative research programs in which NIH investigators cooperate with organizations in foreign countries in specific areas of advanced technology for mutual benefit;
- Serving as a resource for defined laboratory animals;
- Assisting in ensuring the long-term availability of nonhuman primates for biomedical research;
- Providing training opportunities in laboratory animal science for foreign scientists;
- Developing programs to train technicians in scientific instrument repair; and
- Establishing repair and maintenance (R & M) centers for hospital equipment in several foreign countries.

Highlights of Recent Scientific Advances Resulting From International Activities

Through DRS, a Collaborative Research Agreement in magnetic resonance imaging (MRI) was created between the NIH and Thomson-CGR in France. Under the agreement, the NIH has received a Magniscan 5000 MRI system to investigate the utility and potential of MRI in the field of oncology and to assess general diagnostic imaging applications of MRI. The 0.5 tesla MRI system, installed in the Diagnostic Radiology Department of the NIH Clinical Center, offers unique capabilities such as intra-voxel incoherent motion imaging in addition to the conventional MRI modes available on other MRI systems at the NIH. The investigator who invented the intravoxel incoherent motion methodology is currently an NIH Visiting Associate.

Bilateral Agreements and Other Country-to-Country Activities

Caribbean Islands: Under a Participating Agency Service Agreement with the Agency for International Development (AID), the Biomedical Engineering and Instrumentation Branch (BEIB) of DRS has participated in a joint effort with Project Hope. This project was designed to improve the R & M capability of the biomedical equipment maintenance program of the Jamaican Ministry of Health at the College of Arts, Science, and Technology in Kingston and to develop

a cooperative regional program for the repair and maintenance of hospital clinical care equipment for the islands of Barbados, St. Lucia, St. Vincent, Montserrat, St. Kitts, Antigua, Dominica, and Grenada. In Jamaica, BEIB provided technical assistance in the repair and maintenance of specialized groups of equipment and trained instructors for a portion of the training program at Kingston.

BEIB's program for the Eastern Caribbean strengthened regional capability to repair hospital equipment on each of the major islands and developed a program of mutual assistance in instrument maintenance among the islands. The small amount of equipment on any one of the islands, the variability in the skills needed, and the potential availability of Ministry of Health repair personnel made it impractical to provide each of the islands with repair staff capable of meeting all possible maintenance requirements. BEIB improved the maintenance capability of each of the islands by training local personnel and providing a selection of test equipment, tools, replacement parts, and technical literature. When local personnel cannot perform a repair, they will be able to call for the assistance of a qualified technician from one of the other islands.

The project was completed in September 1987, and maintenance capability in the region has been improved significantly. All of the islands have received a selection of test equipment, tools, supplies, and technical literature, and 11 technicians from the region have been trained in equipment maintenance at the NIH. Equipment maintenance facilities on all of the islands have been upgraded, and the technicians trained at the NIH can be called on to fulfill the majority of the region's equipment maintenance needs. The largest maintenance facility in the region, at the Queen Elizabeth Hospital in Barbados, has been enlarged and is now capable of providing maintenance training to personnel in the region.

Egypt: In April 1980, an agreement was signed between the Egyptian Ministry of Health and the U.S. Department of Health and Human Services. Under the Special Foreign Currency Program, the Egyptian Ministry of Health, with the cooperation of BEIB, made plans to develop a pilot R & M center for medical equipment. This center was planned to service Ministry of Health medical facilities in Giza and to serve as a model for other regional centers to be established throughout Egypt. Implementation began in 1981, with the training of center personnel (both in Egypt and at the NIH), the purchase of equipment and supplies, and the construction of a building to house the center on the grounds of the Hwamdia Hospital. The center became operational in 1982. It operates on a fee-for-service basis; a portion of its income is used to supplement the salaries of its staff. Since its opening, the center has grown and has recently enlarged its facility to keep pace with the increase in workload.

About a year ago, AID provided additional funds for continued work on this project for 2 years. During this period, BEIB is continuing to assist the Hwamdia Hospital center in the development of a program to train equipment users in the proper operation of a variety of hospital equipment.

France: A member of BEIB serves on a board of scientific counselors to review life science research programs conducted in France by the Commissariat à l'Energie Atomique (French Atomic Energy Commission). He also serves on the editorial board of a journal published in Europe, *Innovation and Technology in Biology and Medicine*. The same BEIB investigator also played a key role in initiating and developing the Collaborative Research Agreement on Magnetic Resource Imaging between the NIH and Thomson-CGR and bringing this important gift of advanced technology to the NIH.

Instrumentation and Biomedical Engineering were included as topics under Article 2 of the 1984 Memorandum of Understanding relating to cooperation in the field of biomedical sciences between the NIH and the Institut National de la Santé et de la Recherche Médicale (INSERM) in France.

Activities during FY 1987 included visits by three INSERM scientists to BEIB to work on projects in cardiovascular dynamics and ultrasound image processing. These visits totaled some 2 person-months. A workshop on these subjects was held at an INSERM laboratory in France in September 1987, and four members of BEIB participated and presented papers. The proceedings of the Workshop will be published by INSERM in March 1988.

Two French Visiting Fellows also are collaborating with BEIB investigators in the areas of hyperthermia and cardiovascular dynamics.

Italy: As part of the U.S.-Italy Science and Technology Agreement, DRS has extended an offer to establish bilateral collaboration with the Italian Ministry of Health in the area of laboratory animals in biomedical research. Specific activities of mutual interest include developing an information system and exchanging information on laboratory animal use in primary health care programs for the diagnosis of human and animal diseases and for the monitoring of environmental contamination.

BEIB has established a collaboration with the Faculty of Engineering of the University of Pisa to explore the properties of certain polyelectrolyte gels. BEIB staff, together with a Visiting Associate, are developing novel techniques for separating mixtures of large molecules and exploring concepts for improving sensors or actuators based on the mechanochemical properties of these gels.

Japan: In April 1980, a collaborative project in laboratory animal science was instituted as part of the U.S.-Japan Non-Energy Cooperative Agreement. Its purpose was to promote the exchange of information on laboratory animal models and other aspects of laboratory animal science and the development and use of uniform international standards for research animals. DRS has responsibility for U.S. involvement in this project.

A principal objective of the project is to develop information on quality control of laboratory animals. Several workshops on this subject have resulted in technical manuals written by scientists from a number of countries. The NIH published *Manual of Microbiologic Monitoring of Laboratory Animals* in FY 1986, and a Japanese-language version was published in Japan. During a meeting held in 1986 to discuss current progress and future directions of collaborative efforts, it was agreed to pursue discussions on the possibility of establishing genetically standardized strains of rats and appropriate techniques to monitor the genetic integrity of rat strains. There was also a general discussion of interest in the introduction of specific genes and DNA into laboratory mice through natural mating and transgenic procedures and the extensive support functions required for transgenic work. These discussions will continue at a meeting scheduled for November 1987.

Mexico: BEIB is working with the Centro de Desarrollo y Aplicaciones Tecnologicas (CEDAT) to assist CEDAT in the development of its training program for biomedical equipment technicians. CEDAT is the Ministry of Health's central organization for managing biomedical equipment resources.

BEIB's major effort in this area has been the transfer of training programs developed by BEIB to CEDAT. CEDAT instructors first came to the United States, where they participated in BEIB training courses. After completing the courses, they returned to Mexico and translated the training materials into Spanish.

The CEDAT instructors then returned to the NIH, where they presented the training program, in Spanish, to students from a number of Latin American countries. There was a joint student-instructor evaluation after the course was completed. Based on this evaluation, the course was modified and is now being presented on a regular basis in Mexico.

Training at CEDAT will not be limited to Mexicans but will be available to personnel from all of the Spanish-speaking countries of the Americas. The training program will operate on a fee-for-service basis. Tuition charges will be used to cover the cost of presenting and updating the course and replacing equipment and supplies.

BEIB plans to continue cooperation with CEDAT in the development of additional training material and of management infrastructure for the maintenance of biomedical equipment.

Activities With International and Multinational Organizations

The Office of Animal Care and Use (OACU) represents the interests of Federal agencies and the U.S. biomedical research program in several international forums. OACU maintains a liaison with the following organizations:

- Council of Europe and the Ad Hoc Committee for the Protection of Animals;
- International Conference on Health, to exchange information with health providers in other countries on policies and laws related to the care and use of research animals;
- Canadian Council of Animal Care, to formulate animal care and use policy; and
- International Air Transportation Association, to develop international policy for the airline industry on the transportation of animals.

Pan American Health Organization: The Office of Animal Care and Use, through a contract with the Pan American Health Organization (PAHO), has developed projects to establish New World primate breeding centers and conservation programs in Latin American countries. Specific objectives of the contract are:

- To provide expert consultants and advice to Latin American governments interested in developing primate programs;
- To assist in developing national programs of wild primate conservation and management to ensure the perpetuation of natural nonhuman primate resources; and
- To support development of primate breeding stations to produce species important to biomedical research under captive or semicaptive conditions.

The Peruvian National Primate Project includes a breeding station in Iquitos, as well as field management activities. This project has provided tamarins and squirrel monkeys for use in U.S. biomedical activities since 1976. From 1984 through 1987, the project was expanded to include captive breeding and conservation efforts directed toward the owl monkey, a species uniquely suitable for malaria research. The Iquitos programs have supported AID malaria research programs via a Participating Agency Service Agreement. As a result of PAHO activities conducted under the OACU contract, Peru has been the only Latin American country from which nonhuman primates are regularly available for biomedical research and testing.

BEIB also is cooperating with PAHO in the development of a biomedical equipment maintenance resource facility to serve the Spanish-speaking countries of South America. The facility will be located at the Pan American Zoonosis Center (CEPANZO) in Buenos Aires, Argentina.

BEIB recently evaluated the maintenance capability at CEPANZO and maintenance resources and needs in Argentina. Preliminary plans for the facility include the development of a training program for biomedical equipment repair personnel, an R & M facility, and a resource program that will provide technical assistance in establishing and operating maintenance programs. Students from the region will receive theoretical and practical training in the maintenance of biomedical equipment at the center's training facility followed by practical, hands-on experience at the center's maintenance facility.

PAHO has allocated $30,000 for the initiation of a pilot facility at CEPANZO. BEIB is currently working with PAHO to develop a proposal to obtain additional funding for the development of the center.

World Health Organization: The NIH Genetic Resource of Laboratory Rodents has been designated a Collaborating Center for Defined Laboratory Animals by the World Health Organization (WHO) and as an International Nude Mouse Reference Center by the International Council of Laboratory Animal Science. The resource maintains more than 250 stocks and strains of genetically defined and monitored rodents and rabbits and serves as a source of breeding nuclei of animals used by NIH research investigators as well as by the international biomedical research community. In FY 1987, the resource made shipments involving approximately 1,148 animals to investigators in 26 States and 10 foreign countries.

Renovations of Building 14F to provide improved housing facilities for animals in the resource are nearing completion. Cesarean rederivation procedures will be used to move existing animal stocks into the facility to minimize the possibility of disease transmission.

Appendix A

List of Acronyms

AADCs	Asthma and Allergic Disease Centers
ACTH	Adrenocorticotropic hormone
ADA	American Dental Association
AID	Agency for International Development
AIDS	Acquired immunodeficiency syndrome
AMP	Adenosine 3′,5′-cyclic monophosphate
APKD	Adult polycystic kidney disease
ARC	AIDS-related complex
ASN	American Society for Neurochemistry
ATP	Adenosine triphosphate
BCG	Bacillus Calmette-Guérin
BEIB	Biomedical Engineering and Instrumentation Branch
BHLBC	Beijing Heart, Lung, Blood Vessel Medical Center
BIREME	Biomedical Regional Library of Medicine (São Paulo, Brazil)
BOSTID	Board on Science and Technology for International Development
CAMS	Chinese Academy of Medical Sciences
CC	Warren Grant Magnuson Clinical Center
CDC	Centers for Disease Control
CEDAT	Centro de Desarrollo y Aplicaciones Tecnologicas
CEPANZO	Pan American Zoonosis Center
CEPIALET	PAHO/WHO Regional Center for Investigation and Training in Leprosy and Tropical Diseases
CHD	Coronary heart disease
CHF	Congestive heart failure

CISET	Committee on International Science, Engineering, and Technology
COBIOTECH	International Scientific Committee for Biotechnology
COLCIENCIAS	Colombian Fund for Scientific Research
COPD	Chronic obstructive pulmonary disease
CRC	Cancer Research Campaign (United Kingdom)
CSIR	Council for Scientific and Industrial Research
CVD	Cardiovascular disease
DCBD	Division of Cancer Biology and Diagnosis
DCE	Division of Cancer Etiology
DCL	Diffuse cutaneous leishmaniasis
DCPC	Division of Cancer Prevention and Control
DCRT	Division of Computer Research and Technology
DCT	Division of Cancer Treatment
DESY	Synchroton radiation source
DHHS	Department of Health and Human Services
DOS	Department of State
DRIE	WHO Collaborating Center for Diabetes Research, Information, and Education
DRR	Division of Research Resources
DRS	Division of Research Services
EEG	Electroencephalography
ELISA	Enzyme-linked immunosorbent assay
EMBL	European Molecular Biology Laboratory
EMBO	European Molecular Biology Organization
EMRC	European Medical Research Councils
EORTC	European Organization for Research on Treatment of Cancer
EPESE	Established Populations for Epidemiological Studies of the Elderly
ESF	European Science Foundation

FAB	Fragment of immunoglobulin chain that carries the antigen binding site
FDA	Food and Drug Administration
FDI	Fédération Dentaire Internationale
FIC	John E. Fogarty International Center for Advanced Study in the Health Sciences
FIOCRUZ	Oswaldo Cruz Foundation
FRG	Federal Republic of Germany
FWF	Austrian Science Foundation
GCP	German Cardiovascular Prevention Study
GIF	Growth hormone-inhibiting factor
GISSI	Group for the Study of Streptokinase in Myocardial Infarction (Italy)
GMI	Gorgas Memorial Institute
GNHBP	German National High Blood Pressure Program
GRC	Gerontology Research Center
GRF	Growth hormone-stimulating factor
HBV	Hepatitis B virus
HD	Huntington's disease
HDL	High-density lipoproteins
HDV	Hepatitis delta virus
HFV	High-frequency ventilation
HIV	Human immunodeficiency virus
HRP	WHO Special Program of Research, Development, and Research Training in Human Reproduction
HTLV	Human T-cell lymphotrophic virus
IARC	International Agency for Research on Cancer
ICAAC	International Conference on Antibiotics and Anti-Infective Chemotherapy
ICAR	International Collaboration in Acquired Immunodeficiency Syndrome Research

ICE	International Collaborative Effort on Perinatal and Infant Mortality
ICIC	International Cancer Information Center
ICIDR	International Collaboration in Infectious Diseases Research
ICL	International Coordination and Liaison
ICMR	Indian Council of Medical Research
ICMRs	International Centers for Medical Research
ICRDB	International Cancer Research Data Bank
ICRETT	International Cancer Research Technology Transfer
ICS-II	WHO International Collaborative Study of Oral Health Outcomes
ICSTI	International Council for Scientific and Technical Information
IDDM	Insulin-dependent diabetes mellitus
IGF	Insulin-like growth factor
IGT	Impaired glucose tolerance
ILAR	International League Against Rheumatism
IMBB	Institute of Molecular Biology and Biotechnology
INCAP	Institute of Nutrition Central America and Panama
INR	Bacillus Calmette-Güerin
INSERM	Institut National de la Santé et de la Recherche Médicale (French National Institute of Health)
IP_3	Inositol triphosphate
IPCS	International Program on Chemical Safety
IRMA	Immunoradiometric assay
ISN	International Society for Neurochemistry
ITDR	International Tropical Diseases Research
JNCI	Journal of the National Cancer Institute
JWGHC	U.S.-Egypt Joint Working Group on Health Cooperation
LBV	Laboratory of Biology of Viruses
LCI	Laboratory of Clinical Investigation

LCP	Laboratory of Chemical Physics
LDL	Low-density lipoproteins
LH	Luteinizing hormone
LI	Laboratory of Immunology
LID	Laboratory of Infectious Diseases
LIG	Laboratory of Immunogenetics
LIR	Laboratory of Immunoregulation
LMI	Laboratory of Molecular Immunity
LMSF	Laboratory of Microbial Structure and Function
LPD	Laboratory of Parasitic Diseases
LPVD	Laboratory of Persistent Viral Diseases
LRC	Lipid Research Clinic
MAbs	Monoclonal antibodies
MARC	Minority Access to Research Careers
MDAECRD	WHO Collaborating Center for the Methodology, Design, and Analysis of Epidemiological and Clinical Research in Diabetes
MEDLARS	Medical Literature Analysis and Retrieval System
MeSH	Medical Subject Heading
MOMP	Major outer membrane protein
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
MRB	Mathematical Research Branch
MRI	Magnetic resonance imaging
NAAIDC	National Advisory Allergy and Infectious Diseases Council
NCC	Nutrition Coordinating Committee
NCDDG	National Cooperative Drug Discovery Groups
NCI	National Cancer Institute
NCNR	National Center for Nursing Research
NCVDG	National Cooperative Vaccine Development Group

NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHS	German National Health Survey
NIA	National Institute on Aging
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIC	National Informatics Centre (India)
NICHD	National Institute of Child Health and Human Development
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDDM	Noninsulin-dependent diabetes mellitus
NIDR	National Institute of Dental Research
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NLM	National Library of Medicine
NMR	Nuclear magnetic resonance
NSF	National Science Foundation
NTP	National Toxicology Program
OACU	Office of Animal Care and Use
OCs	Oral contraceptives
OCC	Office of Cancer Communications
OECD	Organization for Economic Cooperation and Development
OECI	Organization of European Cancer Institutes
OIA	Office of International Affairs
OMAR	Office of Medical Applications of Research

OPRR	Office of Protection From Research Risks
ORCA	European Organization for Caries Research
PAAO	Pan American Association of Ophthalmology
PAF	Platelet activating factor
PAFAMS	Pan American Federation of Associations of Medical Schools
PAHO	Pan American Health Organization
PCBs	Polychlorinated biphenyls
PDQ	Physician Data Query
PET	Positron emission tomography
PGL	Phenolic glycolipid
PHS	Public Health Service
POMC	Propriomelanocortin
R & M	Repair and maintenance (center)
RDS	Respiratory distress syndrome
RVF	Rift Valley fever
SFCP	Special Foreign Currency Program
SGA	Small for gestational age
SGOMSEC	Scientific Group on Methodologies for the Safety Evaluation of Chemicals
SHR	Spontaneously hypertensive rat
SIDA	CDC/Institute of Tropical Medicine (Antwerp)/Ministry of Health of Zaire Study of AIDS in Zaire
SIDS	Sudden infant death syndrome
SIF	Senior International Fellowship
SOLVD	Studies of Left Ventricular Dysfunction
SPA	WHO Special Program for the Prevention and Control of AIDS
SPRA	WHO Special Program for Research on Aging
STD	Sexually transmitted disease
TDR	WHO/UNDP/World Bank Special Program for Research and Training in Tropical Diseases

TDRU	Tropical Diseases Research Unit
TIMI	Thrombolysis in Acute Myocardial Infarction study group
TMIG	Tokyo Metropolitan Institute of Gerontology
UICC	International Union Against Cancer
UNDP	United Nations Development Program
UNICEF	United Nations International Children's Emergency Fund
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USIF	U.S.-Indo Fund for Cultural, Educational, and Scientific Cooperation
USJCMSP	U.S.-Japan Cooperative Medical Sciences Program
VLDL	Very low density lipoproteins
WHO	World Health Organization

Appendix B Definitions of NIH International Program Activities

Research

Foreign Research Grants

The NIH supports research projects outside the United States only when they have met special criteria established for foreign grants. These criteria include high scientific merit, relevance to the program interests of the NIH, and potential for significantly advancing the health sciences in the United States.

Cooperative Agreements

Cooperative agreements are assistance awards to foreign or domestic institutions in which substantial programmatic involvement is anticipated between the NIH and the recipient during performance of the contemplated activity.

Core Grant to Gorgas Memorial Institute

A core grant to the Gorgas Memorial Institute/Gorgas Memorial Laboratory in Panama is appropriated through the budget of the FIC, NIH. The GML conducts research in tropical diseases of importance to Central America and the United States.

Domestic Grants With Foreign Components

A domestic grant with a foreign component is an NIH-financed grant to a domestic institution in which a part of the grant is used to support research in a foreign country.

International Collaboration in Infectious Diseases Research Awards

Under the International Collaboration in Infectious Diseases Research Program, emphasis is given to developing relationships between U.S. institutions and counterpart institutions abroad in infectious diseases research. The ICIDR Program was begun in 1979, when International Centers for Medical Research, which had existed from 1962, were phased out. In Table I-1, the foreign component of ICIDR awards are reported with other "Foreign Components of Domestic Grants." In Tables I–3 and I–4, total ICIDR awards are reported separately.

International Scientific Meetings

The NIH assists in the support of scientific meetings held to coordinate, exchange, and disseminate information when such activities are directed toward objectives clearly within the area of NIH program interests. Activities reported include international components of those meetings supported under this research program area.

Special Foreign Currency (P.L. 480) Grants

The Special Foreign Currency Program, administered by the FIC, enables the NIH to support overseas activities that contribute to the advancement of health sciences in the United States. Funded by U.S.-owned local excess currency primarily derived from the sale of surplus U.S. agricultural commodities, these activities include biomedical research and the translation and dissemination of scientific literature. Funds for the Special Foreign Currency Program are appropriated to the Department's Office of the Assistant Secretary for Health and awarded and administered by the NIH.

Foreign Contracts

Contracts with institutions outside the United States must comply with special criteria prescribed for such awards.

Domestic Contracts With Foreign Components

A domestic contract with a foreign component is an NIH-financed contract to a domestic institution in which a part of the contract is used for activities in a foreign country.

Scientist Exchanges

Visiting Fellows, Associates, Scientists

The NIH Visiting Program offers talented scientists throughout the world the opportunity to share the research resources of the NIH. Through this program, distinguished scientists at all levels of their careers are invited to the NIH to receive further research training and to conduct research in their biomedical specialties.

International Research Fellowships

The FIC International Research Fellowship Program provides awards to foreign scientists in the formative stages of their careers to come to the United States for up to 2 years to receive advanced research experience. Fellows are required to return to their respective home countries at the termination of their fellowships.

Scholars-in-Residence

The FIC Scholars-in-Residence Program has been developed to facilitate the work of individual scholars and the exchange of ideas among scholars, distinguished science leaders, and science administrators. Scholars-in-Residence are nominated by NIH scientists and spend up to 12 months in residence at the NIH.

Senior International Fellowships

The FIC Senior International Fellowship Program provides opportunities for established U.S. faculty members who have demonstrated productive scholarship and achieved recognized stature in their profession to go abroad to conduct collaborative research and to share their expertise. It is intended that this award be a career-enhancing educational experience with mutual benefits to both home and host institutions.

National Research Service Awards

Under NIH National Research Service Awards, predoctoral, postdoctoral, and special fellowships to promote training for research in health-related sciences are granted each year to U.S. citizens, noncitizen nationals of the United States, or persons who have been lawfully admitted to the United States for permanent residence. With acceptable justification, these fellowships may be taken at foreign institutions. Fellowships are not awarded for study leading to the M.D., D.D.S., D.V.M., or other professional degree.

Foreign Work/Study Assignments

The Foreign Work/Study Program involves overseas work assignments that are developed by NIH professionals not only to meet their own training and experience needs, but also to contribute to the domestic and/or international goals of the Department. Potential assignments are developed directly with foreign institutions, U.S. organizations that have overseas installations, or other appropriate organizations that can provide a foreign work/study experience that would fulfill program objectives.

International Travel

International travel is defined as travel by NIH personnel, traveling under DHHS travel orders, to locations outside the United States, including Canada and Mexico, to attend international meetings or to participate in the activities of multilateral organizations (e.g., WHO, PAHO). This category also includes travel under bilateral exchanges.

Program Support

Bilateral Exchanges

Bilateral exchanges not only contribute to advancement of biomedical and behavioral science for the benefit of health in the United States, but also serve the purpose of:

- Overcoming social or political barriers;
- Fostering sharing of technical resources and expertise;
- Drawing on unique resources or settings; and
- Furthering U.S. foreign policy objectives.

Index by Country/ Area

Abu Dhabi, 73
Africa, 33, 43, 47, 69–71, 90, 139, 143, 145, 152, 162
Algeria, 8, 10, 32, 33, 79, 86
Antigua, 164
Argentina, 6, 8, 10, 28, 32, 33, 54, 68, 73, 90, 94, 99, 103, 104, 107, 112, 127, 136, 144, 166
Asia, 33, 43, 82, 93, 100, 104, 141, 143
Australia, 6, 8, 10, 14, 18, 20, 26–28, 32, 33, 47, 55, 67, 68, 73, 90, 98, 100, 102, 103, 105–107, 113, 114, 117, 123, 126, 128, 129, 135, 136, 140, 141, 144, 147, 151, 152
Austria, 5, 6, 8, 10, 23, 27, 29, 31–33, 68, 73, 95, 102, 104, 156

Bahamas, 8, 10, 32
Bangladesh, 7, 8, 10, 32, 71, 73–74
Barbados, 8, 10, 32, 47, 164
Belgium, 5, 6, 8, 10, 27, 28, 31–33, 35, 39, 40, 55, 67, 70, 74, 90, 94, 95, 102, 104, 113, 121, 125, 126, 144, 152
Bolivia, 8, 10, 28, 68, 74
Botswana, 148
Brazil, 6–8, 10, 23, 27, 28, 31–33, 40, 44–47, 54, 68, 73–75, 77, 89–93, 103, 110, 127, 128, 130, 136, 144, 151
Bulgaria, 6, 8, 10, 18, 23, 29, 31, 33, 75, 144, 152
Burma, 8, 10, 26, 29, 33

Cameroon, 161, 162
Canada, 5, 6, 8, 10, 14, 19, 20, 25, 28, 32, 33, 40, 47, 54–55, 67, 68, 75–76, 90–93, 101, 103, 105, 112–114, 118, 123–127, 135, 136, 138–142, 144, 147–151, 156, 159, 160, 168
Caribbean islands, 70, 88, 151, 163–164
Chile, 8, 10, 28, 32, 33, 72, 76, 77, 90, 103, 104, 127, 129, 138, 143, 144, 151, 152
China, 5–8, 10, 28, 32, 33, 35–37, 40, 44, 47–49, 54–57, 67, 68, 73, 76–77, 90, 93, 99, 100, 102–107, 110–115, 118, 121–124, 126, 127, 130, 132, 136, 140, 141, 144, 145, 148, 149, 151, 152, 156
Colombia, 6, 8, 10, 28, 32, 33, 77, 89, 136, 140, 143, 144, 151
Congo, 47, 71, 90, 152
Costa Rica, 8, 10, 32, 68, 100, 101, 105, 151, 152
Cyprus, 141
Czechoslovakia, 6, 8, 10, 32, 57, 77, 102, 110, 112, 127, 135, 144, 152

Denmark, 8, 10, 27, 28, 32, 33, 39, 90, 100, 103–106, 113, 115, 118, 124, 136, 144, 149, 152
Dominica, 164
Dominican Republic, 8, 10, 48, 77

Eastern Europe, 127
Ecuador, 70, 128, 142
Egypt, 5, 6, 8, 10, 32, 33, 35–37, 40, 68, 72, 73, 77–78, 105, 111, 112, 132, 143, 151, 164
Ethiopia, 8, 10, 28, 32, 33, 78, 89

Europe, 26, 33, 39, 68, 69, 72, 93, 94, 100, 104, 118, 126, 141, 142

Finland, 6, 8, 10, 18, 27, 28, 32, 33, 36, 67, 72, 73, 78, 99–101, 105, 113–115, 118, 124, 127, 128, 132, 136
France, 5–8, 10, 14, 20, 23, 27–29, 31–33, 35–39, 54, 57, 68, 73, 78–79, 90, 102–105, 107, 112–114, 119, 121, 127, 129, 130, 135, 136, 140, 142, 149, 151, 153, 159, 163, 164

Gambia, 79, 85
Germany, Federal Republic of, 5–8, 10, 18, 25, 27, 28, 31–33, 35–40, 54, 55, 57–58, 67, 68, 73, 80, 90, 91, 93, 94, 100, 102–107, 112–114, 118, 129, 135, 136, 138, 142, 144, 150, 151, 153, 156
Ghana, 8, 10, 32, 33
Greece, 6, 8, 10, 28, 32, 33, 58, 68, 80, 93, 94, 97–98, 102–104, 108, 130, 144
Grenada, 164
Guatemala, 99, 101
Guyana, 90

Haiti, 7, 70, 80–81, 161
Honduras, 153
Hong Kong, 8, 10, 32, 33, 90, 103, 144, 153
Hungary, 5, 6, 8, 10, 18, 29, 31–33, 35–37, 58–59, 102–104, 106, 110, 112, 113, 127, 129, 136, 140, 144, 149, 153
Iceland, 8, 10, 32, 68, 144
India, 6–8, 10, 15, 18, 20, 21, 26–30, 32, 33, 37, 39, 43–48, 59, 68, 71–73, 81–82, 86, 90, 95, 99, 102–104, 106, 108, 110–114, 118–119, 126, 127, 129, 130, 132–133, 136, 141, 143, 144, 149, 151–153, 159, 160
Indonesia, 8, 10, 33, 44, 89, 161, 162
Iran, 8, 10, 32, 130, 136, 144
Iraq, 153
Ireland, 8, 10, 27, 28, 32, 33, 90, 103, 108, 141, 148, 153
Israel, 5–8, 10, 20, 26–28, 32, 33, 55, 59, 67, 68, 77, 82, 90, 93, 94, 97, 99–100, 102–107, 111–114, 118, 119, 124–130, 138, 141–144, 146–149, 160
Italy, 5–8, 10, 18, 19, 28, 32, 33, 35–37, 39, 40, 43, 46, 48, 55, 59–60, 67, 68, 73, 90, 91, 95, 102–107, 110, 113, 114, 119, 127, 128, 130, 133, 136, 141, 142, 144, 146, 149–151, 153, 164–165
Ivory Coast, 153

Jamaica, 8, 10, 32, 82, 105, 129, 143, 144, 151, 153, 163, 164
Japan, 5–8, 10, 14, 18, 20, 26–28, 31–33, 35–37, 39, 40, 46–49, 54, 60–61, 68, 72, 73, 82–83, 90, 94, 95, 98, 100, 102–108, 113, 114, 117–121, 124, 127–130, 132, 133, 136, 138, 141, 143–151, 153, 156, 159, 160, 165
Jordan, 8, 10, 32

Kenya, 6, 8, 10, 33, 68, 76, 83, 162
Korea, 6, 8, 10, 28, 32, 33, 37–38, 61, 68, 90, 93, 105, 113, 136, 144, 153
Kuwait, 6, 151, 153

Latin America, 7, 23–25, 31–33, 43, 44, 46–47, 69, 70, 88, 93, 104, 126, 127, 139, 141, 143, 151, 165–167
Lebanon, 9, 11, 28, 32, 83, 136, 144
Luxembourg, 9, 11, 32, 113, 148

Malawi, 153
Malaysia, 9, 11, 32, 33, 48
Mali, 9, 11, 33

Malta, 9, 11, 32
Martinique, 143
Mauritania, 9, 11, 33
Mexico, 6, 9, 11, 18, 21, 25, 28, 32, 33, 61, 68, 71, 72, 74, 83, 90, 93, 101, 103, 104, 110, 127, 129, 139–142, 149, 151, 165, 168
Micronesia, 143
Middle East, 33, 119, 152
Montserrat, 164
Morocco, 32

Near East, 87, 152
Nepal, 106
Netherlands, 9, 11, 19, 20, 27, 32, 33, 84, 90, 93, 100, 102, 103, 105, 107, 112–114, 125, 135, 136, 142, 144, 148, 150, 156, 159, 160
New Guinea, 153
New Zealand, 9, 11, 18, 27, 28, 32, 33, 94, 101, 103, 105–107, 113, 114, 126, 128, 141, 144, 153
Nicaragua, 74
Nieue, 123
Nigeria, 6, 9, 11, 28, 32, 61, 68, 105, 140, 141
North Africa, 119
North America, 26, 84, 118, 141
Norway, 9, 11, 26–28, 32, 33, 84, 90, 98, 100, 101, 103, 110, 113, 115

Pacific Basin, 47, 69, 100, 117, 118, 122, 123, 126, 143, 150
Pakistan, 6, 9, 11, 32, 33, 61, 72, 84, 86, 100, 153
Panama, 84, 167
Peru, 7, 9, 11, 32, 44–47, 84, 89, 90, 111, 127, 153, 166
Philippines, 9, 11, 32, 33, 101–102, 111, 112, 144
Poland, 5, 6, 9, 11, 23, 28–33, 35, 36, 38, 61–62, 68, 73, 84, 90, 127, 136, 144, 149
Polynesia, 123, 143
Portugal, 9, 11, 32, 33, 141, 153

Raretonga, 123
Romania, 5, 6, 9, 11, 29, 31, 32, 55, 67, 127
Rwanda, 84

St. Kitts, 164
St. Lucia, 164
St. Vincent, 164
Saudi Arabia, 9, 11, 32
Scandinavia, 98, 126
Scotland, 98, 100, 118, 129, 135, 157
Senegal, 9, 11, 68, 140
Seychelles, 84, 139, 143
Sierra Leone, 9, 11, 32
Singapore, 9, 11, 32, 103, 104, 153
South Africa, 6, 9, 11, 32, 33, 68, 84, 106, 144, 151, 153
Southeast Asia, 31, 47, 69, 119, 120, 152
Spain, 6, 9, 11, 28, 32, 33, 48, 68, 73, 90, 100, 102–107, 113, 118, 121, 138, 144, 159
Sri Lanka, 6
Sudan, 9, 11, 32, 84, 89, 103
Sweden, 6, 9, 11, 14, 18, 27, 28, 32, 33, 40, 55, 67, 68, 72, 73, 85, 100, 103–106, 112, 113, 117, 118, 127–130, 135, 136, 141, 144, 146, 148, 149, 151, 153, 160
Switzerland, 6, 9, 11, 18–21, 25, 27, 28, 32, 33, 38, 39, 48, 85, 90, 100, 102–104, 112–114, 128, 129, 135, 136, 138, 140, 141, 144, 147, 149

Syria, 33, 107

Taiwan, 6, 9, 11, 27, 28, 32, 33, 38, 66, 68, 73, 86–87, 104, 107, 113, 114, 118, 134, 136, 144, 153
Tanzania, 9, 11, 40, 68
Thailand, 6, 9, 11, 28, 32, 40, 55, 62, 67, 71, 85, 111, 141
Tibet, 44, 47
Togo, 47
Trinidad and Tobago, 86, 143, 153
Tunisia, 9, 11, 32, 90, 141
Turkey, 9, 11, 19, 32, 33, 62, 86, 103

Uganda, 9, 11, 32, 33, 68
United Arab Emirates, 68
United Kingdom, 5, 6, 9, 11, 14, 18–20, 27, 28, 32, 33, 39, 47, 55, 67, 68, 70, 86, 90–95, 98, 100, 102–106, 111–114, 118, 121, 123, 124, 126, 127, 129, 130, 136, 141, 142, 144, 148, 149, 151, 153, 156, 157
United States, 1, 5, 7, 9, 11, 14, 18–20, 23, 25–33, 36–38, 40, 41, 43, 45–50, 54–67, 69–73, 76, 77, 81–83, 88, 90–92, 94, 98–100, 104, 107, 109–112, 115, 117–121, 124, 126, 127, 132, 133, 136, 138–143, 145, 146, 149, 150, 156, 160, 162, 164, 165, 167, 168
Upper Volta, 153
Uruguay, 9, 11, 28, 32, 33
U.S.S.R., 5–7, 9, 11, 23, 26, 29, 31, 33, 35, 36, 38, 54, 62–66, 73, 86, 90–93, 103, 107, 111, 113, 114, 133, 140, 153

Venezuela, 5, 9, 11, 14, 28, 32, 66, 72, 86, 89, 90, 140, 141, 153
Vietnam, 9, 11, 32

Wales, 100, 103, 127
West Africa, 70
West Indies, 43, 47, 68, 153

Yemen Arab Republic, 86
Yugoslavia, 5, 6, 9, 11, 18, 28–33, 66, 104, 107, 108, 112, 118, 127, 134, 144, 150, 153, 159

Zaire, 9, 11, 32, 68, 70, 74, 86, 89, 105, 153
Zimbabwe, 6, 32, 68

Index by International Organization

Commission of European Communities, 31

European Culture Collection Organization, 110
European League Against Rheumatism, 94
European Medical Research Councils (EMRC), 17, 18, 31, 100
European Molecular Biology Organization (EMBO), 93, 94, 121
European Organization for Caries Research, 110, 113
European Organization for Research and Treatment of Cancer (EORTC), 9, 11, 35, 36, 38
European Science Foundation, 31

Family Health International, Inc., 87
Federation Dentaire International (FDI), 110–111

Helen Keller International, 7, 44, 47

International Agency for Research on Cancer (IARC), 5, 9, 11, 35, 38, 39, 79, 134
International Agency for the Prevention of Blindness, 48
International Association for Cataract Related Research, 48
International Association for Dental Research, 113
International Cancer Information Center, 35, 40–41
International Cancer Research Data Bank, 41
International Center for Infectious Disease Research, 161
International Council for Scientific and Technical Information, 151, 152
International Council of Laboratory Animal Science, 166
International Council of Ophthalmology, 48
International Council of Scientific Unions, 19, 135
International Labor Organization, 134
International League Against Epilepsy, 141, 142
International League Against Rheumatism, 121
International Medical Informatics Association, 160
International Program on Chemical Safety, 134–135
International Science and Technology Institute, Inc., 87
International Scientific Committee for Biotechnology (COBIOTECH), 19
International Society for Neurochemistry, 141
International Society for the Assessment of Technology in Health Care, 93
International Sociological Association, 112
International Union Against Cancer (UICC), 35, 38
International Union of Pure and Applied Chemistry (IUPAC), 21

Medical Research Council, 121–122

North Atlantic Treaty Organization (NATO), 19–20, 107

Organization for Economic Cooperation and Development (OECD), 31
Organization of European Cancer Institutes, 35

Pan American Association of Ophthalmology, 7, 44, 47
Pan American Congress of Infectious Diseases, 90
Pan American Congress of Ophthalmology, 48
Pan American Federation of Associations of Medical Schools (PAFAMS), 28
Pan American Health Organization (PAHO), 5, 9, 11, 18–19, 21, 23–25, 30–32, 66, 70, 87, 111, 122, 151, 152, 166, 168
Pan American League Against Rheumatism, 92, 93

Sigma Theta Tau International Honor Society of Nursing, 157

United Nations Development Program (UNDP), 29, 69
United Nations Environment Program, 110, 134
United Nations International Children's Emergency Fund (UNICEF), 93, 115

World Bank, 29, 69
World Confederation for Physical Therapy, 156
World Federation of Neurology, International Research Group on Dementia, 142
World Health Assembly, 19, 31
World Health Organization (WHO), 5, 9, 11, 19–21, 23, 25, 29–32, 40, 43, 44, 47, 49, 55–57, 61, 66, 67, 69–71, 87–88, 90, 100–101, 110–112, 118, 122–123, 126, 127, 134–135, 141, 147, 151, 152, 166, 168
World Hypertension League, 68

Index by Research Area

Acquired immunodeficiency syndrome (AIDS), 7, 19–21, 23–26, 58, 68–71, 73, 74, 79–82, 84–90, 111, 113–115, 130, 143, 156, 161, 162
Adolescents, 64, 101
Adult polycystic kidney disease (APKD), 14, 118, 126
Aged/aging, 14, 120, 144–150
AIDS. *See* Acquired immunodeficiency syndrome.
Allergy, 71, 76, 81, 88, 90, 114
Alzheimer's disease, 14, 139–142, 145–150
Anemia, 62, 70, 79, 101
Animals/animal models, 20, 25–26, 28, 48, 60, 74–75, 78, 81, 85, 113, 121, 125, 126, 131, 132, 146, 148, 163–166
  primates, 31, 65, 79, 89, 104–105, 161–163, 165–166
Ankylosing spondylitis, 121
Arrhythmia, 55, 59, 64, 67
Arthritis, 7, 31, 91–95, 112–114, 121, 156
Asthma, 54, 60, 65, 71, 84
Atherosclerosis, 7, 26, 54, 59–61, 63, 65, 67, 117, 120
Autoimmune disorders, 28, 46, 73, 76, 93–95, 110, 112, 114, 118, 124, 125, 128

Basement membranes, 14, 109, 114
Biochemistry, 103, 128–130
Biofeedback, 65
Biomaterials, 57, 66, 112
Biomedical engineering and equipment, 163–166
Biophysics and physiological sciences, 104, 138
Biostatistics, 56, 147
Biotechnology, 19, 59, 61, 83, 87
Birth defects, 99, 132. *See also* Down syndrome.
Blindness. *See* Eyes/vision.
Blood, 18, 28, 49, 67, 76, 79, 118, 129, 130, 148
  anemia, 62, 70, 79, 101
  blood transfusion and blood resources, 58, 64, 70, 71, 156
Bone, 109, 110, 112–114, 120, 125, 148, 149
  osteoporosis, 91, 93, 94, 110, 120, 147, 148, 150
Bone marrow transplantation, 28, 40

Cancer, 5–6, 14, 26, 31, 35–42, 109, 112, 145, 156
  carcinogenesis, 6, 36–40, 42
    environmental, 36, 39, 40, 82, 103, 132–136
    occupational, 36, 37, 40
    viral, 37, 38, 75, 108
  diagnosis, 27, 37–39, 42, 163

immunology, 39, 40, 76, 86, 125
interventions, 5, 14, 19, 26, 35, 37–40, 42, 74, 109, 141
sites/types:
bone, 109, 110
brain, 59, 141
breast, 36, 40
cervix, 36, 37
choriocarcinoma, 6, 36
colon, 37
esophageal, 6, 35, 36
leukemia, 37, 38, 86, 125
liver, 27, 37, 40
lung, 6, 36, 40
melanoma, 109–110
nasopharyngeal, 37, 38
non-Hodgkin's lymphoma, 37
ocular melanoma, 47–48
oral, 37, 115
penis, 36
prostate, 40
skin, 40
spleen, 27
stomach, 6, 36
testicular, 104
thyroid, 36
Cardiovascular system/cardiovascular disease, 7, 23, 31, 49–68, 102, 141, 142, 149, 164
arrhythmia, 55, 59, 64, 67
artificial heart research, 56, 62, 65–67
atherosclerosis, 7, 26, 54, 59–61, 63, 65, 67, 117, 120
coronary heart disease, 58–63, 123
death rates, 49–52
hypertension, 7, 49, 54, 56, 57, 59–68, 123, 145
ischemic heart disease, 7, 54, 64, 117, 120
lipids, 7, 26, 49, 54–56, 59, 61–63, 65, 67, 98
Cataracts, 7, 43–48
Cellular biology, 21, 28, 61, 65, 68, 107, 108, 112, 121, 128–130, 137
Chagas' disease, 54, 66, 74, 89, 136
Chemicals, toxic. *See* Environmental health.
Chickenpox, 83
Children, 25, 58, 64, 70, 78, 80, 84, 97, 104, 106, 111, 134, 135, 138, 140, 144
diarrheal diseases, 44, 71–72, 78, 80–81
eyes/vision, 44–45, 47
juvenile arthritis, 7, 91–93
nutrition, 44–45, 47, 100, 101, 111
pertussis, 72, 73
respiratory diseases, 44, 60, 77, 87, 106, 152
vaccines, 25, 72, 73, 76, 83, 85, 86
Cholera, 7, 30, 71, 74, 82
Clinical trials, 5, 35, 37, 40, 46–48, 55, 61, 67, 72, 81, 92, 93, 99, 100, 115, 119, 124, 139
Coronary heart disease, 58–63, 123
Cryptosporidiosis, 80–81
Cystic fibrosis, 14, 58, 114, 118, 126, 127
Cystinosis, 105

Dengue, 80, 89
Dental/oral health, 14, 109–115

Diabetes, 14, 20, 27, 47, 48, 101, 112, 114, 117–129
Diarrheal diseases, 7, 30, 44, 71–76, 78, 80–81, 84–87, 89, 152
Down syndrome, 7, 14, 97–98, 140, 146
Drugs, 92, 103, 112, 113, 118, 129, 137–138
  AIDS, 19, 70
  antibiotics, 26, 90
  cancer, 5, 14, 19, 26, 35, 39, 40, 74, 109, 141
  cardiovascular disease/lipids, 55, 59–60, 64
  contraceptive, 98–102
  epilepsy, 141, 142
  infectious diseases, 19–20, 72, 74, 75, 81–85, 90, 136
  malaria, 118, 123

Eales' disease, 45, 46
Ecology, 162
Electromagnetic fields, 133
Electrophoresis, 104
Endocrinology, 98–99, 102–104, 106–107, 112, 121–122, 124–126, 128, 130, 136, 149
Enteric disease, 73, 75, 76, 88, 106
Entomology, 31–32
Environmental health, 27, 31, 36, 39, 40, 58, 62, 71, 82, 103, 131–136, 164
Epidemiology, 24, 47, 56, 91, 101–102, 134, 140
  aging, 145–147, 150
  AIDS/HIV-I infection, 69–71, 74, 83
  cancer, 5–6, 36–38
  cardiovascular disease, 7, 49, 54, 56, 59–61, 63–65
  dental/oral disease, 110, 113–115
  diabetes, 14, 117, 122–124, 126–127
  hepatitis, 81–82
  infectious diseases, 74, 77, 78, 82, 87, 89, 161
  neurological disorders, 141–143, 147, 148
  pulmonary system, 56, 58, 62, 84
  rheumatic diseases, 7, 91–93
  urinary tract stones, 118–119
Epilepsy, 28, 139–142
Eyes/vision, 6–7, 30, 31, 43–48, 74, 125, 128, 129, 144

Family planning, 97–102, 135
Filariasis, 29, 30, 69, 75, 77, 80, 81, 84, 87, 89, 161

Genetic engineering. *See* Biotechnology.
Genetics, 18, 24, 26, 54, 61, 78, 81, 86, 89, 102, 105, 108, 125–126, 128–129, 136–138
  adult polycystic kidney disease, 14, 118, 126
  aging, 145, 149
  cancer, 26, 40
  cardiovascular disease, 62
  cystic fibrosis, 14, 118, 126
  dental/oral health, 111, 112
  diabetes, 117, 123, 124
  Down syndrome, 7, 14, 97–98, 140
  environmental contamination, 103, 131–132, 135
  eyes/vision, 46, 48
  mutagenesis, 82, 108, 132–136
  neurological disorders, 14, 30, 140
Gerontology. *See* Aged/aging.
Glaucoma, 43, 47

Gonorrhea, 75, 85
Graves' disease, 114, 125, 128

Haemophilus influenzae type b, 76, 106
Head injury, 143–144
Hearing, 14, 140
Heart. *See* Cardiovascular system/cardiovascular disease.
Hemophilia, 67
Hepatic system, 24, 26, 84
Hepatitis, 26, 30, 38, 74–76, 78, 80–82, 84, 86, 87, 89, 90, 156
Human development, 97–104, 107, 135
Human immunodeficiency virus I (HIV-I), 7, 26, 54, 57, 58, 70–71, 74–76, 78–81, 83, 84, 88, 130. *See also* Acquired immunodeficiency syndrome.
Human immunodeficiency virus II (HIV-II), 71
Human research subjects, 20
Human T-lymphotropic virus I (HTLV-I), 70, 78, 143
Human T-lymphotropic virus II (HTLV-II), 143
Human T-lymphotropic virus III (HTLV-III), 143. *See also* Acquired immunodeficiency syndrome.
Huntington's disease (HD), 14, 140, 141
Hypertension, 7, 49, 54, 56, 57, 59–68, 123, 145

Immunology, 19, 27, 30, 58, 73–89, 92, 94–95, 103, 105–106, 114, 125, 129, 147, 156
  AIDS, 70, 71, 75, 79
  autoimmunity, 28, 46, 73, 76, 93–95, 110, 112, 114, 118, 124, 125, 128
  cancer, 39, 40, 76, 125
  immunization/vaccine development, 7, 20, 24–26, 30, 45, 47, 70–78, 81, 83, 85–87, 106
Infants, 59, 61, 72, 73, 85, 86, 100, 101, 104, 106, 121, 128, 157
  diarrheal diseases, 71–72, 81
  feeding practices/nutrition, 99–102, 104
  HIV transmission, 70, 71, 83
  mortality, 14, 98, 100
  premature, 55, 67, 98, 100
  sudden infant death syndrome, 101, 102
Infectious diseases, 23, 24, 31, 45, 69–90, 106, 167
Influenza, 76, 86, 88
Information sciences, 15, 29, 38–41, 58–59, 104, 122, 147, 159–160, 163
  data systems, 41, 110, 138, 147, 148
  National Library of Medicine, 15, 151–153
Insulin, 121, 123–124, 127, 128
Ischemic heart disease, 7, 54, 64, 117, 120

Kaposi's sarcoma, 7, 70, 156
Keratomalacia, 45
Kidney. *See* Renal system.

Laboratory administration, design, and safety, 21
Lactation, 101
Leishmaniasis, 29, 69, 73, 74, 77, 81–83, 89
Leprosy, 29, 30, 69, 78, 81, 82, 84, 89, 90
Leukemia, 37, 38, 125
Lipids, 7, 26, 49, 54–56, 59, 61–63, 65, 67, 98, 120, 126, 128
Liver. *See* Hepatic system; Hepatitis.
Lowe syndrome, 105
Lung disease. *See* Pulmonary system/pulmonary disease.
Lupus erythematosus, 28, 94, 95, 121

Lyme borreliosis, 7, 79, 91, 92
Lymphoma, non-Hodgkin's, 37

Malaria, 29, 30, 69, 70, 74, 76, 77, 79–82, 85–87, 89, 90, 118, 123, 161, 166
Measles, 24, 25, 44–45, 47
Meningitis, 77, 84, 85
Mental health/illness, 18
Mental retardation, 97. *See also* Down syndrome.
Metabolic diseases/metabolism, 98, 107, 112, 118, 119, 123, 126–128, 149
Molecular biology, 17, 21, 58, 61, 63, 65, 89, 118, 121, 128, 129, 137, 159
Monoclonal antibodies, 59, 61, 73, 86, 110, 114, 155
Multiple sclerosis, 139, 141, 143
Muscle biology, 91–94
Muscular dystrophy, 30
Musculoskeletal disease, 91
Mycoplasma organisms, 78, 82
Myelopathy, 139, 143

National Library of Medicine, 15, 151–153
Nerve growth factor, 107–108
Neurological disorders and stroke, 14, 26, 139–144, 146
  Alzheimer's disease, 14, 139–142, 145–150
  epilepsy, 28, 139–142
  stroke, 7, 14, 28, 54, 60–61, 66, 67, 139–143
Neurosciences, 18, 23, 28, 31, 59, 102–103, 110, 119, 129, 130, 135, 136, 140–142, 144
Nuclear medicine, 114, 155
Nursing, 157
Nutrition, 6, 20, 35, 36, 40, 60–61, 111, 112, 120–121, 147, 150
  eyes/vision, 44–45, 47, 48
  malnutrition, 82, 100, 101, 104, 111, 119–120
  maternal and child health, 99–102, 104, 111

Obesity, 120, 128
Occupational safety and health, 21, 28, 132
  cancer, 36, 37, 40
  lung disease, 58, 66
Osteoporosis, 91, 93, 94, 110, 120, 147, 148, 150

Pain, 110, 112, 113, 138, 140, 142
Parasitic diseases/parasitology, 23–25, 27, 69, 73, 76, 80, 82, 84, 85, 87, 89, 90, 136
Parkinson's disease, 141, 142
Pemphigus foliaceus, 91, 92
Pertussis (whooping cough), 30, 72–73, 77, 78, 83, 85, 94, 106
Pharmacology. *See* Drugs.
Pneumonia, 30, 77
Poliomyelitis, 24–25
Population research, 97
  aging, 148–149
Pregnancy and childbearing, 14, 70, 83, 97–101, 104, 143
Prevention, 14, 24, 97, 99, 156, 157
  AIDS/HIV transmission, 71, 73, 87
  blindness, 7, 30, 43–48
  cancer, 6, 35, 36, 38–40
  cardiovascular disease, 57, 59–61, 64–66
  dental/oral disease, 110, 111, 113–115
  rabies, 23–26, 90

Psoriasis, 113
Publications, 20, 26, 39, 41, 44, 87, 92, 94, 122, 123, 129, 134, 135, 146–149, 151–152, 165
Pulmonary system/pulmonary disease, 7, 31, 44, 49, 54–63, 65–68, 81, 86, 87, 89, 100, 106, 136
  asthma, 54, 60, 65, 71, 84
  infants and children, 55, 61, 67, 77, 152

Rabies, 23–26, 30, 90
Radiation, 132, 133
Rehabilitation medicine, 156
Renal system, 14, 27, 59, 62, 105, 118–119, 124, 126, 136
Reproductive sciences, 18, 28, 30, 97, 99, 100, 102, 104, 106–107, 121, 135, 136
Research materials, 121–122, 125, 126
Respiratory disease. *See* Pulmonary system.
Retinitis pigmentosa, 46
Rheumatic diseases. *See* Arthritis.
Rickettsial diseases, 69, 76–77, 79
Rift Valley fever, 77, 78, 83
Risk factors for:
  AIDS/HIV infection, 71, 74, 76, 79, 83, 86
  cardiovascular disease, 7, 54, 56, 59–61, 65, 102
  cataracts, 7, 43, 45, 46
  glaucoma, 43, 47
  lung cancer, 36
  preterm delivery, 100
  pulmonary diseases, 62
  small-for-gestational-age births, 101
  stroke, 143
  xerophthalmia, 45
Rubella, 24

Salla disease, 105
Schistosomiasis, 27, 29, 69, 74–76, 83, 84, 87, 89
Sexually transmitted disease, 76, 81, 100. *See also* Acquired immunodeficiency syndrome; Gonorrhea; Syphilis.
Shigellosis, 84, 89
Sickle cell disease, 54, 67, 129
Skin, 40, 71, 76, 91–93, 113, 142
Smoking, 40, 55, 61, 62, 67, 123
Spasmodic torticollis, 144
Spinal cord, 109, 110, 114, 140, 143
Staphylococcus aureus infections, 106
Stroke, 7, 14, 28, 54, 60–61, 66, 67, 139–143
Sudden infant death syndrome, 101, 102
Syphilis, 25, 74, 79

Tay-Sachs disease, 128
Technology, 55, 67, 87, 120–121, 144, 159
  assessment and transfer, 18, 21, 24, 93
  imaging, 20, 21, 59, 155, 160, 163, 164
Thalassemia, 58, 59
Thyroid, 36, 125, 128, 130
Toxicology, 18
Toxopolasmosis, 74, 85
Trichomonas vaginalis, 77
Tropical diseases/tropical medicine, 29, 69, 87–90, 152, 167

Tropical spastic paraparesis, 143
Trypanosomiasis, 29, 69, 73, 74, 76, 77, 84, 89
Tuberculosis, 24, 30, 69, 70, 81, 82, 84, 87, 90
Typhoid fever, 30, 76, 84, 89, 106
Typhus, 77

Urolithiasis, 118–119

Varicella (chickenpox), 83
Vector-borne diseases, 31–32, 69, 74, 77, 79, 83, 86–89
Viral diseases/virology, 19–20, 30, 69, 72, 74–76, 78, 79, 82, 83, 85–90, 108, 114, 123, 128, 142, 143, 162
  cancer, 37, 38, 40, 75
Von Willebrand's disease, 62
Voyt-Koyanagi-Harada's disease, 46
Wilson's disease, 142

Yaws, 23–25

May 1988